

Emergencies in Neurology

Volume I

Mamta Bhushan Singh
Rohit Bhatia
Editors

Second Edition



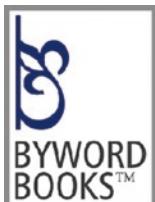
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Preface to the Second Edition

The first edition of *Emergencies in Neurology* came in 2011. We acknowledge the appreciation of many readers, especially younger colleagues and residents, who found the book useful. This encouragement from readers, some inadvertent errors that had crept into the first edition and needed correction and the intervening years where research has led to further progress and availability of new evidence leading to refinement of some treatments made us consider working on a second edition.

The basic format of the second edition remains the same as that of the first. Each chapter includes a discussion outlining a systematic approach to a neurological emergency. This is followed by a comprehensive description of the best management recommended for that emergency. In the second edition, an attempt has been made to update management, keeping in mind the latest evidence that is currently available. Substantive changes have been made in several chapters and minor improvements in others.

The second edition is in two volumes. This has been done to accommodate five new chapters, and one extra chapter created as a previous one became too voluminous and had to be divided into two. The extra new chapters cover important subjects that we were not able to include in the first edition. Distinguished authors have contributed to each of these. We hope that the newly added chapters broaden the scope of this edition and increase its value for the readers.

Neurological disorders may be visualized as forming a wide spectrum with chronic illnesses at one end and acute emergencies at the other. Chronic neurological disorders have a relatively protracted temporal profile during which they provide ample opportunity not just for clinical evaluation and anatomical localization but also for performing numerous investigations at a relatively convenient pace. On the other hand, neurological emergencies are very different in that they appear abruptly, generally have a stormy course and necessitate a rushed and yet balanced approach.

While many voluminous and scholarly textbooks of neurology are available to readers worldwide, having a small, sharp, evidence-based and updated account of how to approach critically ill patients seemed like a good idea to us. Emergency management can be a challenge as well as reap rich dividends if it is understood and practised with maturity, skill and energy. The nihilism associated with neurological emergencies in the past is increasingly being replaced by aggressive emergency management leading to better outcomes. Additionally, in resource-crunched areas of the globe, it may not always be a neurologist who attends to patients presenting

with neurological emergencies. Therefore, it seems logical to have a handbook that is comprehensive and yet not overwhelming in detail.

This book has been conceived and written, keeping in mind the needs felt by a first-contact doctor who may be a neurology trainee, a seasoned or junior neurology consultant, a physician or an intern. Special attention has been focused on the various aspects of management of patients in the emergency department from the point of taking a good clinical history and performing a quick and targeted clinical examination to investigating and starting treatment. The relevant differential diagnoses that should be thought of in various circumstances and how they can be excluded have been dealt with in sufficient detail. A carefully selected list of citations at the end of each chapter will be useful for the reader seeking more advanced and detailed information.

In recognizing and expressing our gratitude to all those who contributed to this endeavour, we must mention that it was a global effort. So while, on the one hand, we had some of our revered teachers and mentors contribute chapters, we also had distinguished international authors, each adding a unique perspective for the reader. Most of the authors are experts in the areas of their contributions, and this reflects in their balanced and valuable opinions. We would also like to concede that drawing of experts from multiple sources does become a challenge in maintaining timelines.

However, every effort has been made to keep the text as updated and contemporary up to the point that we handed over our manuscript to the publisher. We hope that this book will be an asset for all of you who seek answers to questions that arise while you manage neurological emergencies.

New Delhi, India
New Delhi, India

Rohit Bhatia
Mamta Bhushan Singh

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About the Editors and Contributors

About the Editors

Mamta Bhushan Singh has been a faculty member at the All India Institute of Medical Sciences, New Delhi, since 2002. She is currently a professor in the Department of Neurology. Her work is mainly focused on reducing the burden of untreated epilepsy in India. Over the past decade, she has published her research in international journals and made presentations at numerous international meetings. Dr. Singh's ongoing initiative, which provides epilepsy care to rural Indian patients through a mobile clinic on the Lifeline Express, has been highly successful. The American Academy of Neurology selected Dr. Singh as the 2016 Viste Patient Advocate of the Year in recognition of her community work on epilepsy.

Rohit Bhatia has been a faculty member at the All India Institute of Medical Sciences, New Delhi, since 2003, and is currently a professor in the Department of Neurology. His keen interest in stroke took him to the University of Calgary, Canada, where he completed a Fellowship in Cerebrovascular Disorders from the Calgary Stroke Program in 2010. Dr. Bhatia has been working towards improving stroke programs ever since, and his efforts were recognized by the American Academy of Neurology with the 'Safety and Quality' Award in 2015. Dr. Bhatia has published extensively in Indian and international journals, not only on stroke but also on demyelinating disorders, neuromuscular diseases, headache and stem cell therapy. He recently headed the group appointed by the Government of India for formulating the CNS TB guidelines for managing extrapulmonary TB. Most of Dr. Bhatia's current research is in the field of stroke, and demyelinating disorders including an investigation of the interplay between aspirin resistance and ischemic stroke in Indian patients and biomarkers for relapse and disease outcomes among patients with multiple Sclerosis.

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Approach to a Patient in the Neurology Emergency

1

Mamta Bhushan Singh and Rohit Bhatia

In the eight years that have passed since the first edition of *Emergencies in Neurology* was published, science has continued to make progress and our understanding and management of neurological emergencies has further evolved. There are areas that have gained more prominence with better investigation techniques and a wider availability of tests that were once possible only in a handful of research laboratories. This is especially relevant for the immune-mediated diseases including the autoimmune encephalitides. A new chapter on autoimmune encephalitis has therefore been added to the second edition. Several other chapters that have been added belong to areas that are not actually new but were either inadvertently missed in the first edition or were left out due to constraints of space. With the addition of several new chapters, we have split the second edition into two volumes.

A neurological emergency, similar to that of any other organ system, comes with its own share of challenges and the need to make the right therapeutic decisions—with a race to meet deadlines. Neurological emergencies, although dreaded entities, nevertheless provide an opportunity for astute clinicians to not only hone and test their clinical skills but also to be rewarded with a good outcome in the face of what appear to be insurmountable odds. To achieve this, clinicians need to be able to think on their feet. While it is essential to remain abreast of the most current recommendations and guidelines published in the literature, it is also necessary to remember that each patient presenting to the emergency is a unique individual and what may be applicable to the majority may not necessarily apply to him or her. In the chapters that follow, the reader will find comprehensive descriptions of the most commonly encountered neurological emergencies. The authors will address key issues for each type of neurological emergency.

A patient presenting with a neurological emergency may or may not be in a position to give an account of the illness. Yet, it is imperative to get background

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information, whether it is directly from the patient or from the person accompanying the patient or a bystander who may have witnessed the illness in whole or in part. It is worth spending a few extra moments considering who the best person would be for taking the history, especially in case the patient is not in a condition to participate in this exercise in any way. It is intuitive that nobody is likely to be more informed about a sick child than the mother and she may be the best person to talk to if she is available. Similarly, a spouse staying with the patient may be far more informative than a distant cousin or uncle. Patients' relatives, especially in the Indian context, are prone to presenting the best-dressed and most articulate person available for giving the history. However, this person may not always be the best informed. So, be careful. Obtaining a relatively good initial history of the patient overrides the issue of time. More errors are made in the emergency room, not because of the nonavailability of some sophisticated equipment or a new drug or a profoundly knowledgeable doctor but more often because a simple question remains unasked. The history obtained during the initial contact is likely to evolve further, be edited and supplemented in time. So, to ensure that the patient enters the correct diagnostic 'loop' and is not subjected to futile investigations, the need to make a correct 'first impression' through a succinct history cannot be overemphasized.

Performing a quick, abbreviated and yet comprehensive clinical examination, including a neurological examination, is a crucial step at the time of initial patient contact; more detailed examinations are inevitably performed during the course of the patient's hospital stay. The first evaluation is important because just like the history, this too decides what kind of investigations are prioritized and performed. For example, missing pupillary asymmetry in a patient may unnecessarily delay investigations that are likely to confirm his condition while some other non-essential tests are being done.

Frequently, the patient presenting to the emergency may appear critical with a variably altered level of consciousness. The assumption that a quick neurological examination in such a patient is unlikely to provide any significant clue to the diagnosis, and choosing to rush the patient off for a CT scan instead, may be a lost opportunity. Occasionally, signs picked up by attention to detail in the first examination, such as nuchal rigidity in a stroke-like presentation or subtle facial or eyelid myoclonia in a patient with an unexplained alteration of sensorium and no reliable eyewitness account, may actually clinch the diagnosis and save precious time.

Following completion of the initial history and clinical examination, investigations need to be ordered. Planning and ordering investigations for patients presenting with neurological emergencies also deserve special consideration especially vis-a-vis the therapeutic order when more than one investigation is deemed necessary. Because patients suffering from a neurological emergency are very sick, they should be moved in the hospital as purposefully and precisely as possible. For example, two trips to the radiology department can be reduced easily to one if both a CT scan and an X-ray chest are required. Also, the order in which investigations are conducted is an important consideration. For example, those tests from which the maximum yield is expected and are also easier to perform in a sick patient should precede the more time-consuming ones, especially if their expected yield is also not high. A

more detailed account of the use of radiological investigations, CSF analysis and EEG can be found in Chaps. 2 and 3.

Alteration of sensorium, which may be with or without accompanying fever, could be considered the sine qua non of neurological emergencies. Irrespective of what may be causing an alteration in the sensorium, a patient presenting in such a condition to the emergency will generally be seen by none other than the neurologist on call. So, it is important for neurologists to know about the diverse neurological and non-neurological causes that can lead to encephalopathy and coma and how a clinical differentiation may be made between them on the basis of the history, physical signs and laboratory investigations. Chapters 4 (Coma and Encephalopathy) and 5 (Fever with Altered Sensorium) address these issues.

Acute disorders related to visual disturbances often reflect a neurological origin, although some may be purely ophthalmological. A thorough understanding of the anatomy of the visual pathways is essential for correctly localizing a lesion of the visual system. Chapter 7 is devoted to a discussion of acute visual disorders. The anatomical basis of various entities is discussed, as well as nuances in the clinical presentation, on the basis of which the level of the visual axis affected can be deduced. These are described and the recommended management is presented.

Chapter 8 reviews seizure-related emergencies, which constitute a large proportion of neurological emergencies. Patients with seizures may present to the emergency room in many different clinical contexts, including the first-ever seizure, a breakthrough seizure after remaining stable on anticonvulsants for a variable extent of time, failing to regain consciousness after a prolonged seizure, serial seizures and status epilepticus, amongst others. Each of these situations presents unique diagnostic and therapeutic challenges to the neurologist. Recognizing all forms of status epilepticus and intervening expeditiously cannot be overemphasized.

A common symptom presenting at neurology outpatient clinics is headache. Some headaches, as discussed in Chap. 9, may be severe enough for the patient to present to the emergency room. Such headaches are a mixed bag; some are merely severe presentations of a relatively benign condition, whereas others are harbingers of a more serious neurological illness. Eliciting a good history will help greatly in the initial triage of these patients, especially if a note is made of the previous occurrence and character of the headaches. It is better to err on the side of over-investigation when there is the least doubt about the aetiology of the headache in a patient presenting to the emergency department. Likewise, it is worth considering that the presentation of a headache, like all other pain symptoms, is vastly influenced by the patient's perception. For instance, a patient may be relatively stoical about the pain, whereas another with similar symptoms may be very dramatic about it. The physician should at all times be objective when evaluating different types of patients.

Transient ischaemic attack (TIA), acute ischaemic stroke, intracerebral haemorrhage and cerebral venous thrombosis are dealt with in Chaps. 10, 11, 12 and 13; they constitute a significant proportion of neurological emergencies. These vascular diseases present in a spectrum ranging from the seemingly innocuous, brief and evanescent symptoms of a TIA to the life-threatening presentations of a large

middle cerebral artery or basilar artery occlusion. The vascular diseases, especially a subset of acute ischaemic strokes, for which we now have evidence of therapeutic benefit from timely thrombolysis, are those neurological emergencies for which ‘time’ is critical. This is the situation where the patient is evaluated in a series of steps all proceeding in parallel rather than in tandem. Hence, while the patient is being readied or wheeled into radiology, the history is being verified concomitantly with the examination. Each moment is crucial to the eventual outcome of patients who undergo thrombolysis, and it is crucial to bear this in mind at all times in the emergency room for the best possible outcome.

Meningitis and viral encephalitis are dealt with in Chaps. 14 and 15. These are not just diseases that are commonly seen in the emergency room but are also situations/conditions where a timely diagnosis and treatment often results in a good outcome. While evaluating patients with these conditions, it is useful to keep in mind the geographical area from which the patient comes, any history of recent travel, the season of the year and the immunological status. These factors may have a bearing on the patient’s susceptibility to infections and provide a clue to the infectious agent. Cerebrospinal fluid examination, utilized almost uniformly in the diagnostic algorithm of CNS infections, is dealt with in Chap. 2. The last chapter of volume I of this edition is a new chapter—on chronic meningitis. This deals with chronic meningeal pathologies other than tubercular meningitis.

Volume II of the second edition starts with two new chapters that were not present in the first edition. Chapter 17 deals with neurological emergencies encountered in tropical infections, whereas Chap. 18 deals with autoimmune encephalitis. With increasing international travel and the global village that we have come to inhabit, ‘tropical’ neurological emergencies are no more restricted to the tropics. A neurologist anywhere in the world may be faced with an emergency that is listed here amongst tropical neurological emergencies. Acute CNS demyelinating disorders have been comprehensively covered in Chap. 19. These can either present as a monophasic illness such as acute disseminated encephalomyelitis (ADEM) or transverse myelitis or recurrently in patients with multiple sclerosis and can have confusing and varied manifestations mimicking infective illnesses. Early recognition is essential for appropriate therapy.

Spinal cord disorders, which may be amenable to medical or surgical treatment, can have acute presentations. The anatomical characteristics of the spinal cord, with all ascending and descending tracts travelling to and from the brain traversing through the cord in a dense pattern, make even small lesions of the cord result in grave deficits. Prompt recognition and treatment of these lesions may minimize deficits. The anatomical features of the cord also help in localizing the lesion in terms of the horizontal and vertical levels. A thorough clinical examination of a patient presenting with a spinal cord disease helps in correctly deciding on the level that needs to be focused on while the cord is imaged. Whereas acute spinal cord diseases are discussed in Chap. 20, details about imaging of the cord may be found in Chap. 2.

Neuromuscular emergencies are described in Chap. 21. Many neuromuscular disorders can eventually present with a common endpoint of paralysis; a careful

elicitation of the history and a thorough physical examination are mandatory for a logical conclusion and investigation of the patient. A patient waking up with abdominal pain, ptosis and generalized weakness could indeed have suffered a snake bite; an acute, catastrophic presentation of myasthenia could just be a severe respiratory distress. A high index of suspicion is often required to narrow the differential diagnoses. Most such patients require prompt stabilization and critical care, especially ventilatory assistance. Timely and correct diagnosis and treatment strongly influence the outcome.

Emergencies resulting from movement disorders, covered in Chap. 22, can be fascinating and intriguing. An acutely grimacing patient in great discomfort could be suffering from a drug-induced dystonia or a psychogenic movement disorder. A patient with known parkinsonism and a new-onset confusion and altered behaviour is likely to be suffering from drug toxicity, although a multitude of causes, such as subdural haematoma, stroke and infections, will also need to be excluded. Many movement disorder emergencies are drug-related, either because of too much or too little of the drug or its adverse effects.

Chapters 23, 24 and 25 cover new areas not dealt in the previous edition. Patients are frequently put on long-term immunosuppression to combat various immune-mediated diseases. Then there are others who may be immunocompromised due to infections such as HIV, Chronic renal failure, malignancies and even old age may weaken the immune status of an individual. In all these situations, there may be neurological emergencies that are otherwise not encountered in immunocompetent individuals. These diseases are dealt with in Chap. 23. Although pregnancy is a physiological state, there is a significant alteration of the internal milieu during pregnancy accompanied by significant compensatory efforts of the body to withstand these changes. In the course of all that is happening, some disease states may also occur, and some of these may be emergencies including some neurological emergencies. These emergencies associated with pregnancy are discussed further in Chap. 24. A timely recognition and treatment of these emergencies are crucial both for the health of the mother and the baby. In Chap. 25, neurological emergencies arising out of substance use have been included. An increasing number of individuals are falling prey to substance abuse and with it come various other diseases including neurological emergencies, which are often not emphasized in various training programmes. An awareness and competence in handling these emergencies would be a very useful skill to possess.

Sometimes cancer patients being treated with chemotherapeutic agents also have acute neurological illnesses, ranging from encephalopathy and seizures in the well-characterized posterior reversible encephalopathy syndrome (PRES) to an acute myelopathy. Most of these illnesses are treated symptomatically, but a prompt recognition and withdrawal of the offending agent are imperative. Acute neuro-oncological emergencies are covered in Chap. 26.

There are several neurological emergencies where, in addition to medical management, prompt neurosurgical intervention may be indicated. This is an area in which team work and good neurosurgical support are vital. The initial patient evaluation and assessment of the need for neurosurgery are, of course, within the ambit

of neurology care, but once the need for surgical intervention is felt, it is important to not waste time and seek neurosurgical input urgently. Most situations, such as a raised intracranial pressure, which is dealt with in Chap. 6, or all other situations requiring urgent neurosurgical intervention, as discussed in Chap. 27, are time-sensitive. If surgery is not immediately indicated, what is undoubtedly required is a close clinical watch and periodic assessments to ensure that the neurosurgeon intervenes as soon as it is required. These are situations in which a close collaborative effort and shared responsibility between the neurologist and neurosurgeon are needed.

There are many toxins with proven neurotoxicity of a greater or lesser degree. Exposure to such toxins leads to presentations that may be indolent and have a chronic course on the one hand or to those that may be relatively acute and present as neurological emergencies on the other. These toxin-related emergencies are elaborated in Chap. 28.

In critically ill patients who present with neurological emergencies and do not have an optimum outcome, declaration of brain death, if such a situation arises, can be challenging. A thorough evaluation is needed to rule out mimics, as well as carefully ascertain signs of brain death. Additionally, the physician is faced with a philosophical and legal dilemma and has to work within the ambit of laws permitting withdrawal of life support. The issue becomes all the more important in view of organ donation. These challenges are covered in Chap. 29.

In conclusion, neurological emergencies demand a quick clinical assessment and rapid initiation of treatment, keeping in mind that many diverse conditions may present in a similar manner. We hope that the addition of several new chapters along with a revision of the previous ones to include the most recent, state of the art information necessary for managing neurological emergencies will make this second edition a useful book for you.



Neuroimaging in Neurological Emergencies

2

Ajay Garg and Leve Joseph

Imaging plays a key role in supporting clinical diagnosis in acute neurological emergencies and guiding clinical management of these patients. This chapter gives an overview of the imaging features in different acute neurological syndromes.

Stroke

A cerebrovascular accident or stroke is defined by an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. Pathologically, the process may be an ischaemic or a haemorrhagic event.

Ischaemic Stroke

Ischaemic stroke is secondary to an arterial occlusion and accounts for ~80% of all strokes. Acute cerebral ischaemia may result in a central, irreversibly infarcted tissue core surrounded by a peripheral region of dysfunctional cells known as the penumbra. This region of the penumbra is a dynamic entity that exists within a narrow range of perfusion pressures and is potentially salvageable with early recanalization [1, 2]. Until recently, the purpose of imaging was to differentiate ischaemic stroke from haemorrhagic stroke and to rule out other mimics of stroke, such as a tumour, infection and others. The development of new treatment options, intravenous and intraarterial thrombolysis, and the concept of penumbra have driven the

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development of functional imaging techniques, for example, brain perfusion imaging. The imaging manifestations of cerebral ischaemia vary significantly with time. A comprehensive evaluation may be done with a combination of computerized tomography (CT) and magnetic resonance imaging (MRI) techniques.

CT in Acute Stroke Evaluation

With its widespread availability, ease and speed of use, low cost, non-invasiveness and safety, CT has been a traditional first-line imaging modality for the evaluation of patients with acute stroke.

Non-contrast CT (NCCT)

Several early ischaemic changes (EIC) can be identified in strokes that have occurred <4–6 h earlier (Table 2.1). With proximal middle cerebral artery (MCA) occlusion (Fig. 2.1), the insular region shows loss of definition of the grey–white interface (loss of the ‘insular ribbon’), and the lentiform nucleus shows an obscured outline (obscuration of lentiform nucleus). In addition, an acute thrombus in an intracranial vessel may appear as an area of increased density (‘hyperdense artery sign’) [3–5]. A hyperdense MCA sign also may be seen in the presence of a high haematocrit level or MCA calcification, but in such cases the hyperattenuation is usually bilateral [3–5]. Similarly, thromboemboli in the distal MCA (M2 or M3 branches of the MCA) create punctate hyperdensity, also known as the ‘MCA dot sign’. Whereas the sensitivity of these changes is compromised by their subtlety, interobserver reliability can be improved by systematic CT scan evaluation using systems such as the Alberta Stroke Program Early CT Score (ASPECTS) [6].

The ASPECTS is a topographical scoring system that divides the MCA territory into ten regions of interest on the basis of functional importance (localization weighted) rather than extent. The ASPECTS is determined from two standardized axial CT cuts, one at the level of the thalamus and basal ganglion and the other adjacent to the most superior margin of the ganglionic structures, such that they are not seen (Fig. 2.2). The MCA territory is allotted ten points on these two sections.

Table 2.1 Early ischaemic changes (EIC) on non-contrast computerized tomography

- Loss of ‘insular ribbon’ (differentiation of grey from white matter)
- Obscuration of lentiform nucleus (hypodensity of lentiform nucleus)
- Hyperdense arteries (most commonly proximal MCA or MCA sylvian ‘dot’)
- Loss of cortical grey–white matter differentiation
- Hemispherical sulcal effacement
- Local compression of lateral ventricles

MCA middle cerebral artery

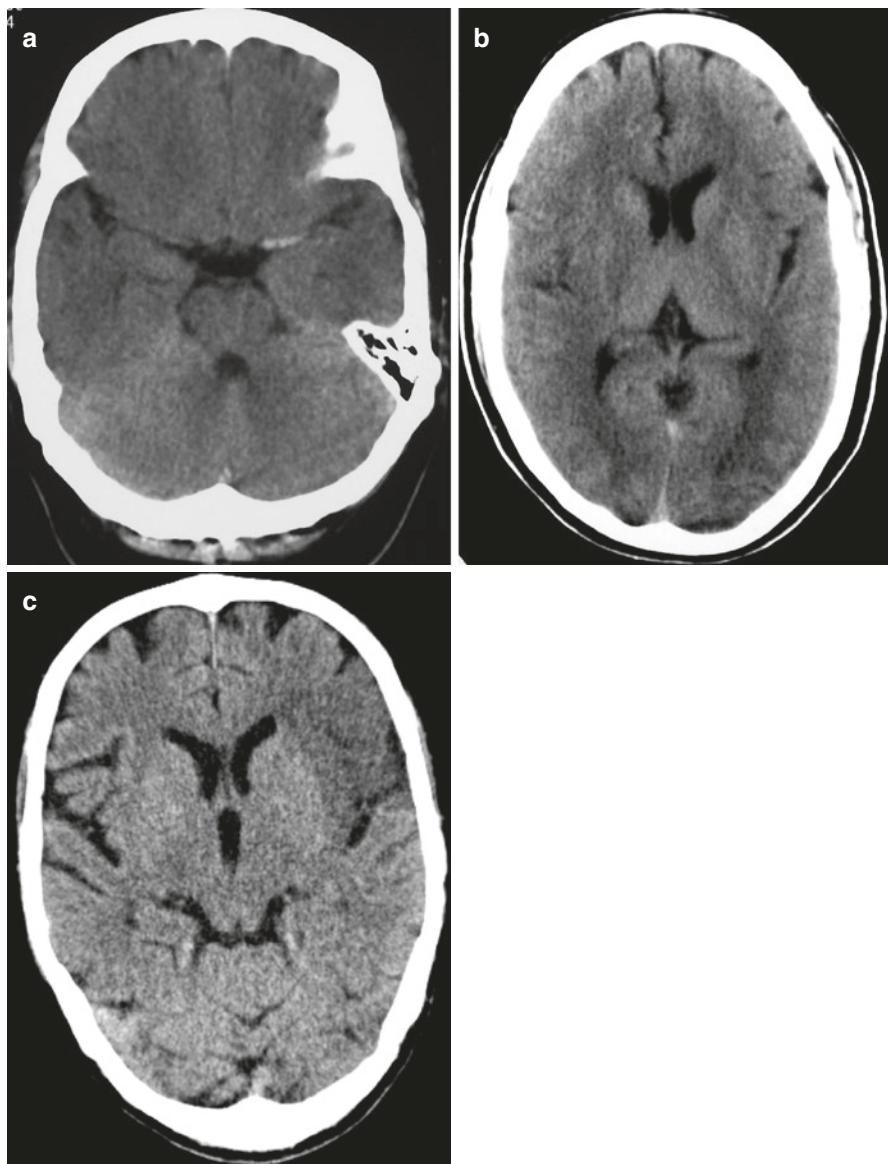


Fig. 2.1 Early ischaemic changes. NCCT scans show hyperdensity of left MCA (black arrow) (a), dense MCA sign; loss of outline of right lentiform nucleus (black arrow) compared to left side (white arrow) (b), obscuration of lentiform nucleus; loss of left insular cortical ribbon (black arrow) compared to right side (white arrow); and loss of grey–white matter differentiation in left frontal operculum (c)

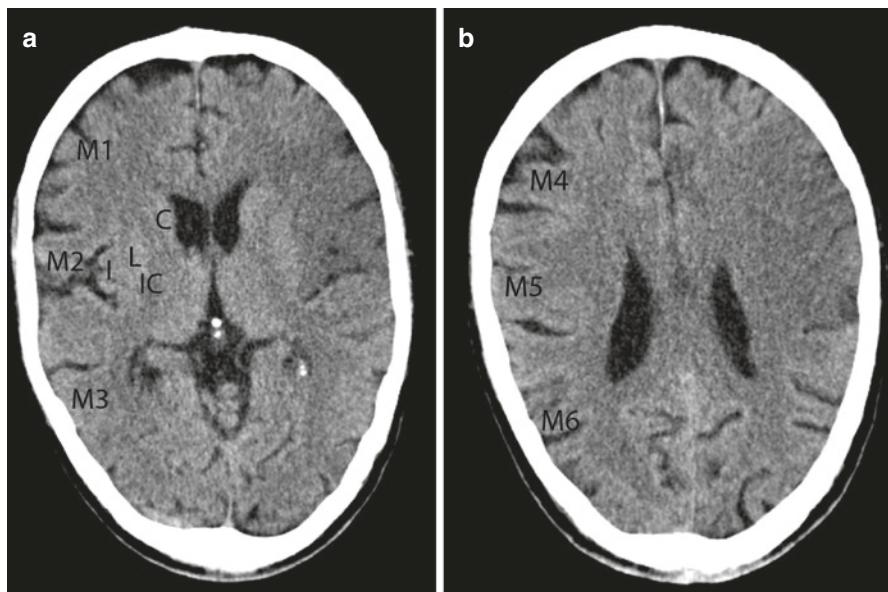


Fig. 2.2 ASPECTS scoring system. NCCT at level of thalami and basal ganglion (a) and just above the level of basal ganglion (b) shows ten ASPECTS-defined regions [M1–M6, I (insula), IC (internal capsule), L (lentiform nucleus) and C (caudate)]. In this case acute infarct in left MCA territory has ASPECTS of five points

To compute the ASPECTS, a single point is subtracted from 10 for any evidence of EIC (e.g. focal swelling, parenchymal hypodensity) for each of the ten ASPECTS-defined regions (M1–M6, I [insula], IC [internal capsule], L [lentiform nucleus] and C [caudate]). A normal CT scan receives an ASPECTS of ten points. A score of zero indicates diffuse ischaemic involvement throughout the MCA territory. The ASPECTS provides a more accurate, robust and practical method for assessing acute ischaemic stroke than the one-third MCA rule and helps in the prediction of clinical outcome [7, 8]. Additionally, ASPECTS can be used as a reliable and convenient surrogate for visual interpretation of lesion volume on CT angiographic source images and diffusion-weighted MR images [9].

After the first 24–48 h, large vessel infarcts are visible on NCCT as wedge-shaped areas of decreased attenuation that involve both the grey and white matter in a typical vascular distribution (Fig. 2.3a). Mass effect initially increases and then begins to diminish after 7–10 days. Enhancement can often be seen in a subacute infarct; typically, a patchy or gyral enhancement pattern may appear as early as 3 or 4 days after ictus and persist for 8–10 weeks.

Contrast CT

The use of intravenous contrast administration does not provide additional information in most cases and is not necessary unless it is required for CT angiography (CTA) and CT perfusion.

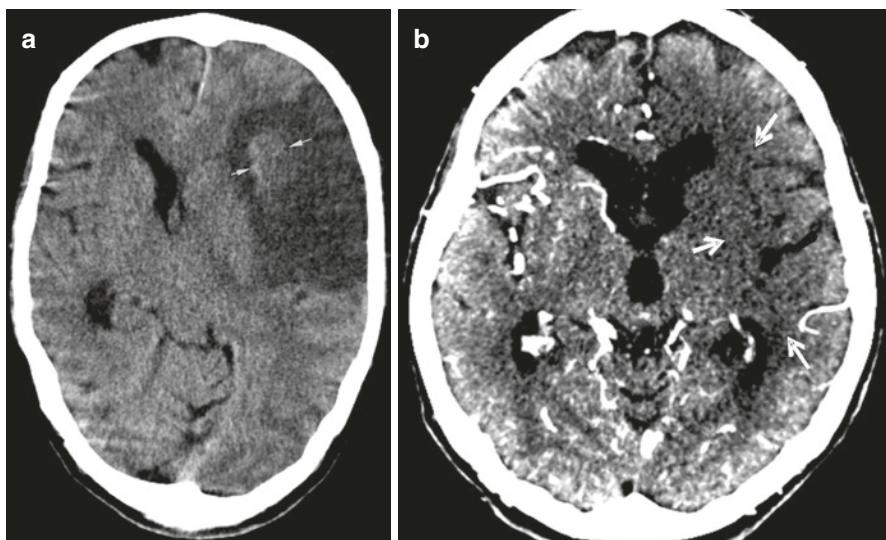


Fig. 2.3 (a) Acute infarct on CT. NCCT shows acute infarct in left MCA territory with area of haemorrhagic transformations (arrows). (b) CT angiography source image (CTA-SI) shows hypoattenuation in the region of left MCA territory indicative of ischaemic change

CT Angiography (CTA)

CTA of intracranial vessels can help in identifying the site of vessel occlusion, assessment of the collateral status and triaging patients for endovascular thrombectomy, which may be of value in clinical management decisions. For example, the response to intravenous thrombolytic treatment of tandem occlusions of the ipsilateral ICA and MCA, of carotid 'T' occlusions or of basilar artery thrombosis is poor compared with isolated MCA occlusion, and the acute recanalization rates of proximal occlusion in general are lower with intravenous recombinant tissue plasminogen activator (rt-PA); many centres considered this a potential indication for rescue therapy with intraarterial thrombolytics or mechanical embolus removal [10, 11]. Furthermore, the identification of carotid artery disease and visualization of the aortic arch may provide clues to the cause of the ischaemic event. CTA can be performed immediately following NCCT without much delay. With the wide availability of modern multi-slice CT scanners, CTA is fast and safe and can be performed without screening for renal function. A dynamic multiphasic CTA is a new technique, performed generally in three phases which include the early arterial, late arterial and venous phases [12]. The arterial phase depicts the exact site of the large vessel occlusion (M1 MCA, ICA, basilar, or vertebral arteries) which is the main criteria for the selection of patients for endovascular thrombectomy. It also gives information on tandem lesions, status of the carotid artery disease at the bifurcation, the type of aortic arch pattern and branching pattern of MCA on the contralateral side, which are important factors influencing the planning and execution of the endovascular thrombectomy. The late arterial and venous phases help to evaluate

the collateral status beyond the site of large vessel occlusion. There are many different collateral grading systems based on different modalities such as CTA, MRI or conventional angiography. The most commonly used are the collateral score of the Society of NeuroInterventional Surgery (formerly the American Society of Interventional and Therapeutic Neuroradiology)/Society of Interventional Radiology (ASITN/SIR) and the Alberta Stroke Program Early CT Score (ASPECTS) on collaterals. ‘The presence of good collateral vessels is more likely to be associated with a smaller core and more salvageable brain tissue and a strong predictor of good outcomes’ [13]. Further, on delayed scan the distal segment of the occluded vessel may be visualized by retrograde filling from the collaterals, and this gives an idea about the length of clot burden which can be used in selecting the hardware during the procedure.

The source images of the brain during CTA acquisition (CTA–SI), compared with NCCT scans, could be more sensitive in detection of early irreversible ischaemia and more accurate for predicting final infarct volume (Fig. 2.3b) [9].

Perfusion CT (PCT)

Patients with a large infarct core are unlikely to benefit from endovascular therapy as against those with small core and significant penumbra. The ischaemic penumbra is defined as brain tissue that will die if untreated but survive if reperfused and can be assessed with either MR perfusion or CT perfusion. PCT is a dynamic contrast-enhanced technique that requires rapid imaging. The basis of CT perfusion imaging is the tracking of the iodinated contrast bolus injected through the cerebral circulation via sequential spiral CT scanning. Two types of perfusion techniques are currently available. Whole-brain PCT provides a map of cerebral blood volume (CBV), and it is postulated that regions of hypodensity on these CBV maps represent the ischaemic core [14]. Although this technique has the advantage of providing whole-brain coverage, it is limited by its inability to provide measures of cerebral blood flow (CBF) or mean transit time (MTT). Alternatively, the second technique, dynamic PCT, has the potential to provide absolute measures of CBF, MTT and CBV. Recent reports demonstrate a high degree of sensitivity and specificity for detecting cerebral ischaemia with both of these PCT techniques [15–17]. Currently available MDCT scanners allow whole-brain coverage with typically 20–30 dynamic scans taken following bolus contrast injection during a CT perfusion examination. Using this cerebral blood flow (CBF) and cerebral blood volume (CBV), mean transit time (MTT) maps can be derived. Matching areas of reduced CBF and CBV correspond to the infarcted core, while areas of CBF and CBV mismatch (reduced CBF and normal or increased CBV) and increased MTT are identified as penumbra [18]. PCT has been validated against other techniques, such as diffusion and perfusion MRI [9, 19–22] and quantitative positron emission tomography (PET). Current guidelines state that the benefits of additional imaging beyond CT and CTA such as CT perfusion or diffusion- and perfusion-weighted imaging, for selecting patients for endovascular therapy, are unknown (*Class IIb; Level of Evidence C*). Further randomized, controlled trials may be helpful to determine whether advanced imaging paradigms employing CT perfusion, CTA and MRI

perfusion and diffusion imaging, including measures of infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are within 6 h of symptom onset but have poor ASPECTS (<6) or those who are beyond 6 h from symptom onset [23].

High-dose contrast administration for CTA or PCT carries a potential risk of allergic reactions and renal impairment but should not preclude its use in a correctly selected patient. The NCCT, CTA and PCT imaging can be used in combination for a quick, comprehensive and accurate evaluation of acute stroke.

MRI in Acute Stroke Evaluation

The role of MRI in the evaluation of patients with cerebrovascular disease is expanding. MRI can provide a gamut of structural and functional information in a stroke patient. Yet, typical time delays associated with an MRI examination limit its role in acute stroke management. However it can serve as an essential problem-solving tool in selected cases. Hence, many acute stroke care centres have started installing dedicated MRI within or in the close vicinity of neurointerventional suites. A typical MRI stroke protocol includes DWI, FLAIR, T2* Gre or SWI, ToF MRA of the circle of Willis and perfusion-weighted imaging (PWI) which can be completed in approximately 10–15 mins.

Conventional MRI

MRI has been shown to be more sensitive in the detection of acute infarct compared with CT, with almost 80% of infarcts being detected within the initial 24 h of ictus [24]. During the initial few hours of ischaemia, the findings on MRI are related to vascular occlusion and its effects on the brain parenchyma in the form of cytotoxic oedema. The former may produce absence of normally visualized flow void in the affected vessel and slow flow with intravascular arterial enhancement following contrast administration [25]. The changes in the brain parenchyma include high T₂ and FLAIR signal intensity, loss of grey–white differentiation on T₁-WI and subtle mass effect (Fig. 2.4). Over the next few days, the signal alteration and mass effect become more conspicuous. This is followed by resolution of intravascular enhancement, reduction in mass effect and appearance of parenchymal enhancement. Gradient echo sequences have the ability to detect clinically silent prior microbleeds not visualized on CT. Although it has been suggested [26–28], though not proven [29], that the presence of baseline microbleeds could be a risk factor for haemorrhagic transformation after antithrombotic and thrombolytic therapy, this hypothesis is yet to affect clinical management.

DWI and PWI

DWI is highly sensitive to ischaemia, perhaps with ‘>95% sensitivity within the first hours, and changes are documented within minutes of symptom onset in humans’ [30]. It is particularly valuable in the early evaluation of patients who might be treated with rt-PA or other acute interventions (Fig. 2.5). In ischaemia, energy

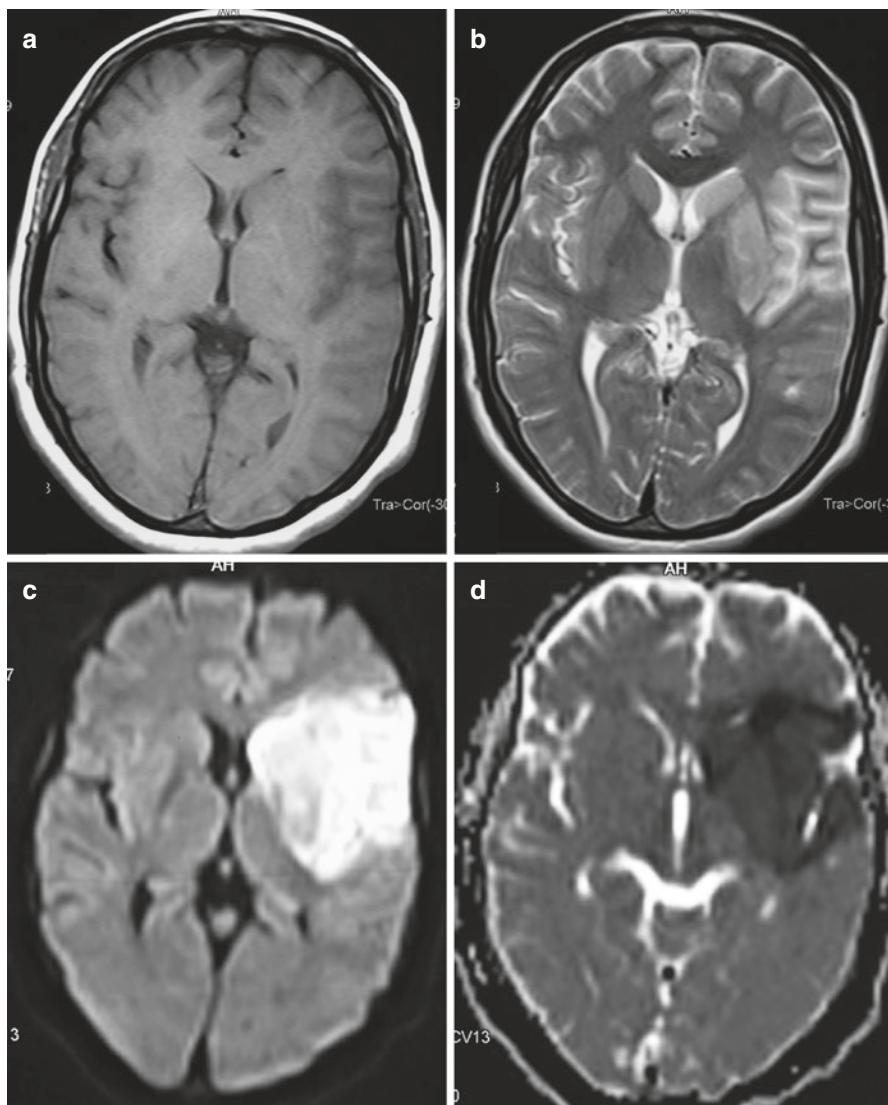


Fig. 2.4 Acute infarct on MRI. Signal changes involving both grey–white matter are seen in left MCA territory. These appear hypointense on T₁- (a) and hyperintense on T₂-WI (b) and show restricted diffusion on DWI (c) and ADC maps (d)

failure compromises cellular ion pumps that normally extrude sodium, resulting in the entry of sodium and extracellular water into cells (cytotoxic oedema). This is evident as a reduced apparent diffusion coefficient (ADC) signal (intracellular water can diffuse less freely than extracellular space water), which is processed to show as bright on DWI. DWI changes are not specific, however, and can be seen in focal seizures, encephalitis and possibly also migraine. Interpretation should also take into account the phenomenon of T₂ shine-through—a term denoting visibility on

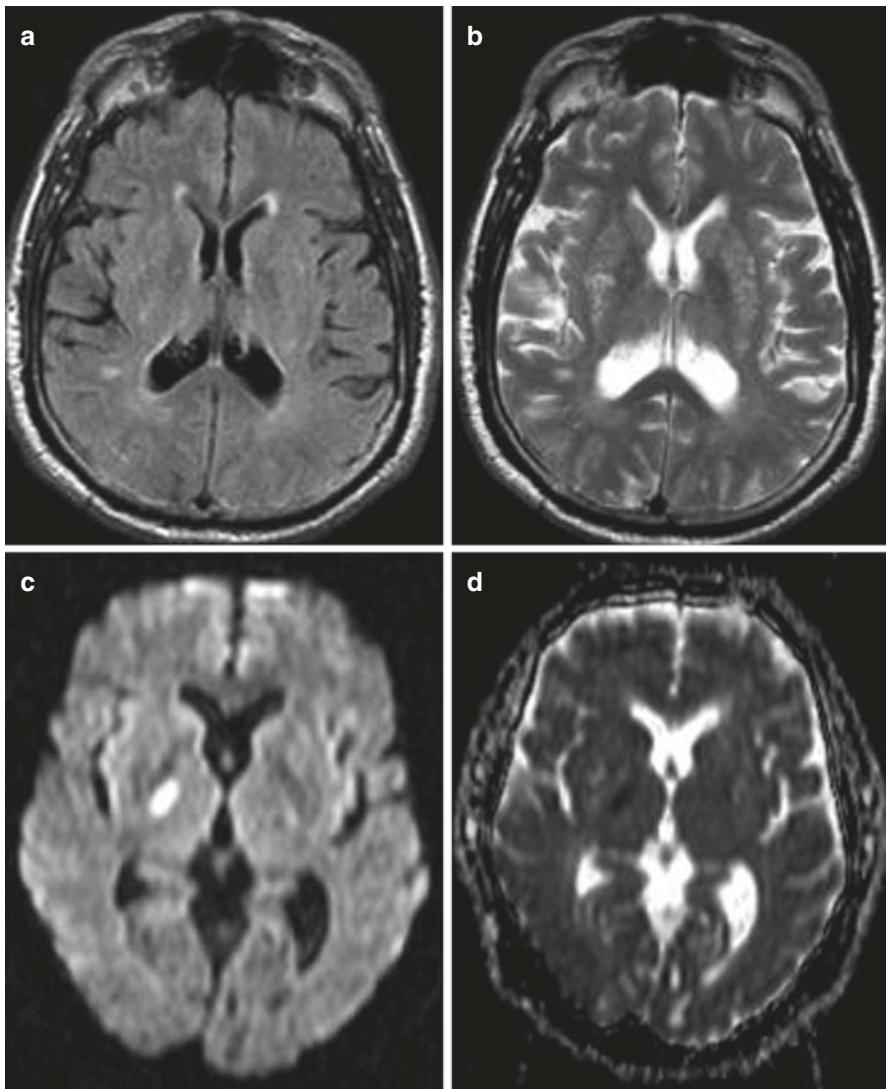


Fig. 2.5 A 65-year-old man presented with left hemiparesis of 4 h duration. Axial FLAIR (a) and T₂-WI (b) does not show acute infarct in the posterior limb of right internal capsule, which appears hyperintense (black arrow) on DWI (c) and hypointense (white arrow) on ADC map (d), suggesting restricted diffusion

DWI of non-acute lesions that are bright on T₂-WI. To confirm whether a DWI lesion represents acute ischaemia, an ADC map should be examined to ensure that the ADC is reduced correspondingly, appearing as a dark signal. The increased DWI signal gradually fades over 7–10 days (depending on the severity of ischaemia and on lesion volume) to an isointense background; thus, DWI is most useful in differentiating recent from remote ischaemia (Fig. 2.6). In patients with a very small

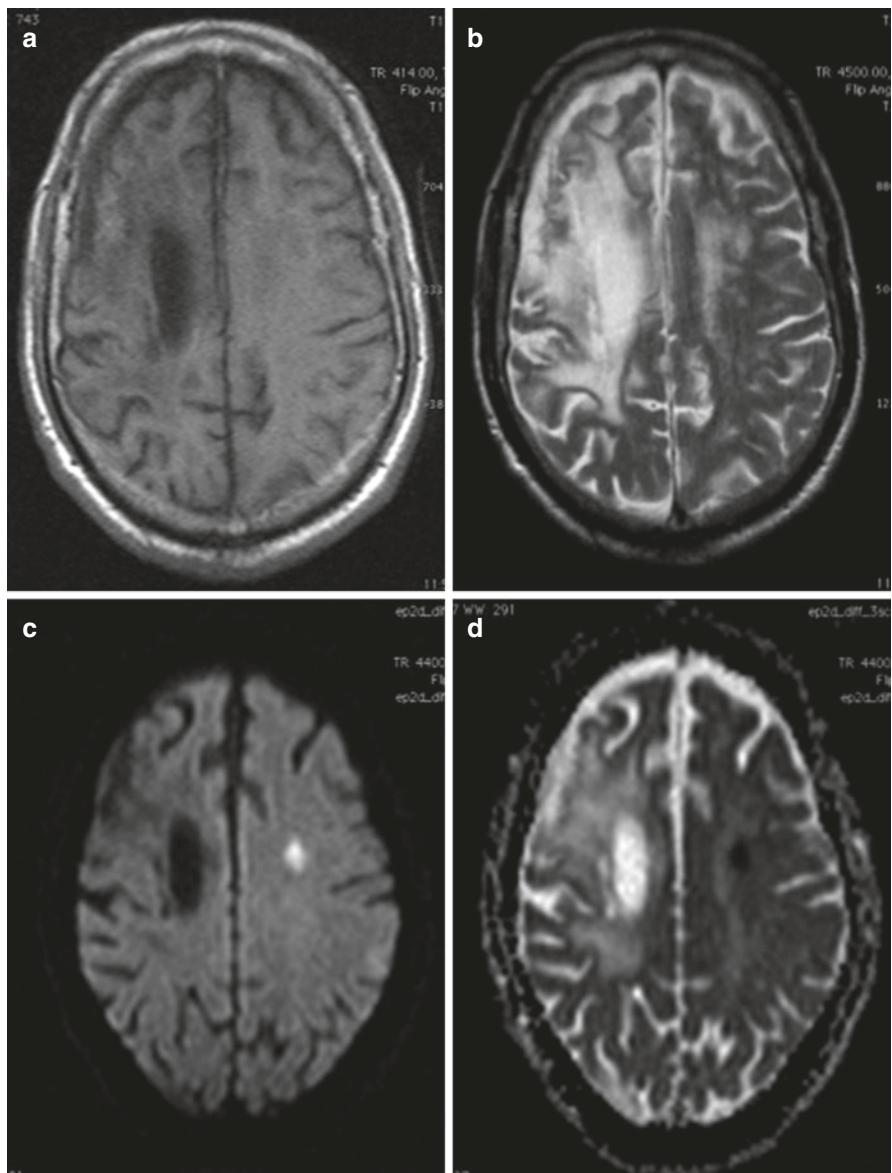


Fig. 2.6 T₁- (a) and T₂-WI (b) show ischaemic lesions in both frontal lobes without any differentiation between acute and chronic lesions. DWI (c) and ADC maps (d) show a focal area of restricted diffusion (black arrow in c and white arrow in d) in left deep frontal matter suggesting acute ischaemic lesion, while the rest of the lesions have increased diffusion suggesting chronic ischaemic lesions

lacunar brainstem infarction or deep grey nuclei infarction, DWI findings may be false-negative [31, 32].

Perfusion MRI is most commonly applied as bolus tracking during the intravenous administration of gadolinium, with the same principles as those governing PCT imaging, allowing the derivation of TTP, MTT, CBV and CBF.

The DWI–PWI Mismatch Hypothesis

The ischaemic penumbra is roughly approximated on MRI as regions of perfusion change without a corresponding diffusion abnormality (diffusion–perfusion mismatch). A DWI–PWI mismatch is present in perhaps 70% of acute strokes caused by MCA occlusion imaged within 6 h of onset, the PWI lesion (hypoperfused) being larger than the DWI ('infarct core'). Over time, the DWI lesion expands to eventually incorporate most of the PWI defect. The mismatch appearance is therefore a potential tool to select patients in whom there is evidence of potentially salvageable tissue (penumbra), either for clinical trials or for individualized treatment. However, the mismatch between DWI and PWI overestimates the volume of the penumbra, partly due to reversibility of initial diffusion abnormality but, more importantly, to inaccuracies in the assessment of perfusion values [33, 34]. PET has shown that the volume of mismatch often is not in agreement with the volume of increased oxygen extraction fraction [35].

Despite these controversies, PWI–DWI remains of great clinical value for selecting patients who might benefit from thrombolysis after 3 h [36–38] or with tandem occlusion of the internal carotid artery and the MCA [39] and for estimating the risk of symptomatic intracerebral haemorrhage in potential candidates for thrombolysis [40, 41].

FLAIR/DWI Mismatch

In acute stroke, appearance of abnormal FLAIR signal intensity is much delayed after the stroke onset (typically >4.5 h). A mismatch in FLAIR/DWI images (bright in DWI and normal in FLAIR) is likely to be within the therapeutic window for institution of treatment (<4.5 h) safely and effectively [42]. Furthermore, a positive ivy sign in FLAIR images, seen as hyperintensities along the subarachnoid spaces of the cortical sulci, is due to sluggish blood flow in the leptomeningeal collaterals due to a proximal stenosis or occlusion. This can be used as a surrogate marker for status of leptomeningeal collaterals and hence a positive predictor of good outcome in stroke treatment [43, 44].

T2* GRE or SWI Imaging

This technique is highly sensitive to susceptibility effect of haemorrhages in the brain parenchyma. The presence of microhaemorrhages within the infarct core is associated with increased risk of haemorrhagic transformation after stroke

treatment. Hypointense signals with blooming artefacts along the major vessels in the cisterns on gradient echo (GRE) image, also called susceptible vessel sign (SVS), is an important biological marker for assessing the nature and burden of clot [45].

MRA

In the early stages of stroke, MRA can locate the site of arterial occlusion in much the same manner as CTA. Time-of-flight (ToF) MRA does not require contrast but takes longer to perform and therefore is often difficult in patients with acute stroke. Contrast-enhanced MRA improves the quality of imaging and shortens imaging time.

A potential diagnostic advantage of MRI over CT has been shown in non-tPA situations in suspected stroke. MRI has an edge in (1) identifying acute, small cortical, small deep and posterior fossa infarcts; (2) distinguishing acute from chronic ischaemia; (3) detecting subclinical satellite ischaemic lesions that provide information on stroke mechanism; and (4) spotting chronic microbleeds [46–49]. Other advantages include greater spatial resolution and the avoidance of exposure to ionizing radiation and iodinated contrast. Limitations of MRI in acute settings include cost, relatively limited availability of the test and patient contraindications, such as claustrophobia, cardiac pacemakers or metal implants. On the other hand, stroke CT is less time-consuming and less costly and is more widely available in emergency departments. Moreover, it is easier to monitor patients in the CT room.

Despite these concerns, careful selection of sequences ensures that multiparametric MRI is well tolerated and widely used in acute stroke and is the primary investigation of choice in many stroke centres worldwide.

Haemorrhagic Stroke

This accounts for 15% of all strokes and is classified as intracerebral haemorrhage (ICH; two-thirds) and subarachnoid haemorrhage (SAH; one-third), depending on the location of haemorrhage.

Non-traumatic ICH

Neuroimaging studies are required not only for diagnosis but also for providing insights into the type of haemorrhage, the underlying aetiology and the accompanying pathophysiology. NCCT is the gold standard for the diagnosis of ICH, and at many centres it is still the modality of choice for assessment of ICH, owing to its widespread availability and rapid acquisition time.

CT Findings

On NCCT, acute intracerebral haematoma typically appears hyperdense with associated mass effect, depending on the size and location of the haematoma (Fig 2.7a, b). A rapidly accumulating haematoma and an unretracted semi-liquid clot may result in hypodense areas within generally hyperdense acute haematomas, the so-called swirl sign. Sometimes acute haematoma may be isodense if there is severe anaemia, impaired clot formation due to coagulopathy or volume averaging with adjacent haematoma. A fluid level within the clot can also occur. This is more common in haematomas caused by anticoagulation but is not specific. They have also been described in haematomas caused by hypertension, trauma, tumour or arteriovenous malformation (AVM). More than 33% of patients with ICH have substantial haematoma expansion when imaged within 3 h of onset, and the expansion is associated with a poorer outcome [50]. It has been found that contrast extravasations on CTA especially the ‘spot sign’ are found to be an early predictor of haematoma expansion [51].

MR Findings

The appearance of ICH is more complicated and more time-dependent on MR than on CT scans. The MR signal intensity of haemorrhage depends mainly on both the chemical state of the iron atoms within the haemoglobin molecule and the integrity

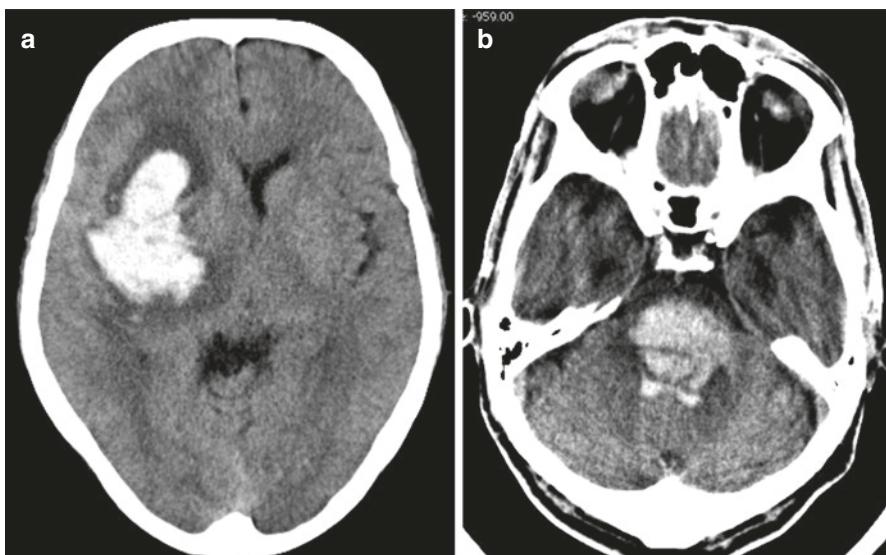


Fig. 2.7 Hypertensive haematoma. NCCT shows acute haematomas in the right external capsule/putamen (a) and pons (b)

of the red blood cell (RBC) membrane. In practice, there is considerable variability in the orderly progression of haematoma signal change over time. It is common to see different stages appear simultaneously. For these reasons, ‘dating’ of the bleed onset using MRI data alone is intrinsically imprecise. Table 2.2 depicts the CT and MR findings in various stages of ICH.

Aetiology Based on Location of the Haematoma and Age of the Patient

Anatomical location and age of the patient are relevant in determining the aetiology of primary ICH (Table 2.3).

Pattern Recognition Clues to the Aetiology of ICH

It may be possible to predict the cause of ICH on the basis of the age of the patient and the distribution and imaging characteristics of the haematoma (Table 2.4).

Table 2.2 Temporal evolution of intracerebral haemorrhage on computerized tomography (CT) and magnetic resonance imaging (MRI; 1.5 T)

Approximate stage	CT	Clinical biochemical forms	T ₁ -weighted MRI	T ₂ -weighted MRI
Hyperacute (<12 h)	Hyperdense	OxyHb in RBCs	Isointense or mildly hyperintense	Hyperintense
Acute (12 h–2 days)	Hyperdense	DeoxyHb in RBCs	Isointense or hypointense	Hypointense
Early subacute (2–7 days)	Hyperdense	MethHb in RBCs	Hyperintense	Hypointense
Late subacute (8 days–1 month)	Isodense	Extracellular MethHb	Hyperintense	Hyperintense
Chronic (>1 month)	Hypodense	Haemosiderin	Isointense or hypointense	Hypointense

Hb haemoglobin, *RBCs* red blood cells

Table 2.3 Aetiology of intracerebral haemorrhage based on location of haematoma and age of patient

Location	Aetiology
Pons	Hypertension, ^a cavernoma, ^b arteriovenous malformation ^b
Basal ganglion/external capsule	Hypertension, ^a vascular malformations ^b
Lobar	Cerebral amyloid angiopathy, ^a hypertension, ^a arteriovenous malformation ^b
Intraventricular	Hypertension, ^a anterior communicating artery aneurysm, anticoagulation, vascular malformation, ^b moyamoya disease (adult), intraventricular neoplasm
Cerebellum	Hypertension, ^a arteriovenous malformation, ^b cerebral amyloid angiopathy ^a

^aOld age

^bYoung patient

Table 2.4 Pattern recognition clues to the aetiology of intracerebral haemorrhage

	Location	Imaging	Comments
Hypertension (Fig. 2.7)	External capsule/ putamina, thalamus, pons	Acute haematoma with classical imaging findings	Suggest angiography for putaminal haemorrhage unless patient >55 years old and hypertensive
Cavernoma (Fig. 2.8)	Pons—favourite location; abuts pial or ventricular surface	'Popcorn-like' lesions on T ₂ -WI with hypointense rim	May be associated with developmental venous anomaly; scan best after intravenous contrast
Haemorrhagic transformation of infarct	Haemorrhage localized to cortex	Non-haemorrhagic component within arterial territory	
Venous infarct	Haematoma in white matter or white matter–grey matter junction	Evidence of CVT, diffusion—variable	Parasagittal region if thrombosis superficial or bithalamic if thrombosis in deep venous system; posterior temporal lobe if occlusion of vein of Labbe
Cerebral amyloid angiopathy	Lobar bleed, spares basal ganglion	Multiple haemorrhages of different ages	Old age
Neoplasm	Anywhere in brain	Non-haemorrhagic component; heterogeneous; delayed evolution of signal changes; multiple stages of haematoma in same lesion; absent, diminished or very irregular hypointense rim; persistent perihematomatous oedema and mass effect; inappropriate enhancement in acute lesion	
Aneurysm	Medial frontal lobe (ruptured anterior communicating artery or anterior cerebral artery aneurysm) and temporal lobe (ruptured MCA aneurysm)	Parenchymal haematoma seen in 4–19% of patients with SAH caused by saccular aneurysm	When ICH is immediately adjacent to subarachnoid space at base of brain or basal interhemispheric fissure, vascular imaging should be strongly considered to exclude saccular aneurysm
Trauma	Orbitofrontal regions, anterior temporal lobes	The presence of fluid–blood level; evidence of head trauma—scalp haematoma, subdural/extradural haematomas	
AVMs (Fig. 2.9)	Anywhere in brain	Suggestive but not sensitive imaging findings include dilated feeding and draining vessels on MR T ₂ -WI, CT angiography, or MR angiography, as well as patchy enhancement	Young age

AVM arteriovenous malformation, MR magnetic resonance, CVT cerebral venous thrombosis, SAH subarachnoid haemorrhage

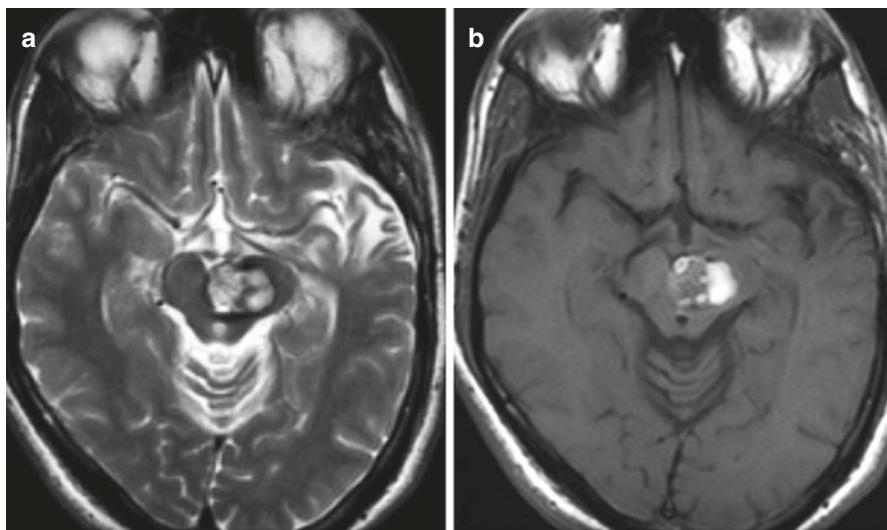


Fig. 2.8 Midbrain cavernoma. The lesion has a mixed signal intensity core with a hypointense haemosiderin rim on T₂- (a) and T₁-WI (b)

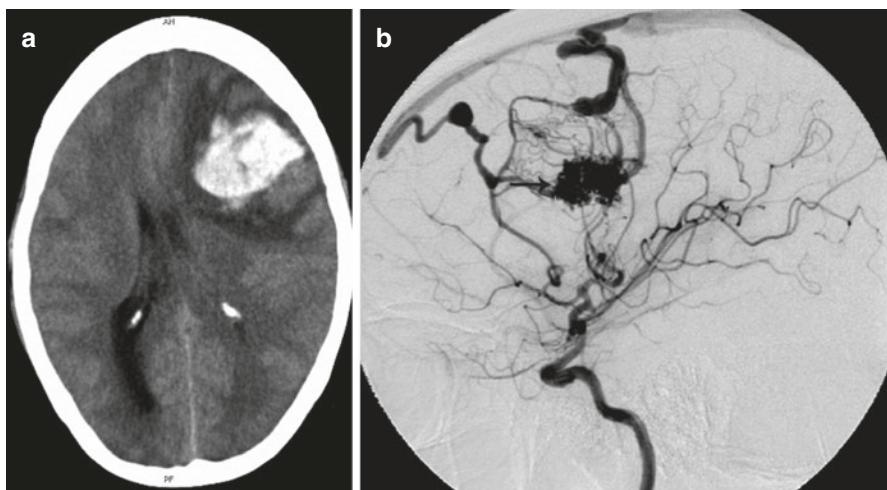


Fig. 2.9 Arteriovenous malformation. NCCT (a) shows an acute haematoma in the left frontal lobe with surrounding oedema and mass effect. Digital subtraction angiography (DSA) (b) reveals a small AVM in the frontal region draining into cortical veins

SAH

SAH is a serious condition that accounts for 5% of all strokes [52]. The clinical hallmark of SAH is a history of unusually severe headache of sudden onset in a previously well patient, especially when it is associated with meningism. The most

common cause of a non-traumatic SAH is an aneurysm rupture. The differential diagnosis of non-aneurysmal SAH is broad, including perimesencephalic non-aneurysmal SAH, AVMs, tumours, pituitary apoplexy, cerebral venous thrombosis (CVT), vasculitis, haematological conditions (including leukaemia and coagulopathies) and drugs (including cocaine, ephedrine and amphetamine).

Imaging of SAH

If SAH is suspected, NCCT is the first line of investigation to confirm the presence of SAH. Acute SAH appears as a hyperdensity in the cerebrospinal fluid (CSF) spaces (Fig. 2.10a). In the first 12 h after SAH, the sensitivity of CT for SAH is 98–100%, declining to 93% at 24 h, [53, 54] and to 57–85% 6 days after SAH [55, 56]. When the CT scan is negative in a patient with suspected SAH, diagnostic lumbar puncture (LP) for analysis of the CSF is strongly recommended [57]. In addition, CT scan can provide important information about the potential complications of SAH, which includes hydrocephalus, infarcts secondary to vasospasm, etc. A false-positive diagnosis of SAH on CT is possible in the presence of generalized brain oedema, with or without brain death, which causes venous congestion in the subarachnoid space mimicking SAH (Fig. 2.11) [56, 58].

MRI techniques using FLAIR images have improved the diagnosis of acute SAH (Fig. 2.12) [59, 60]. However, MRI will not replace CT in the near future as a routine investigation for patients suspected with SAH because of the practical limitations of MRI in the emergency setting (availability, logistics, including difficulty in scanning acutely ill patients, sensitivity to motion artefact, patient compliance,

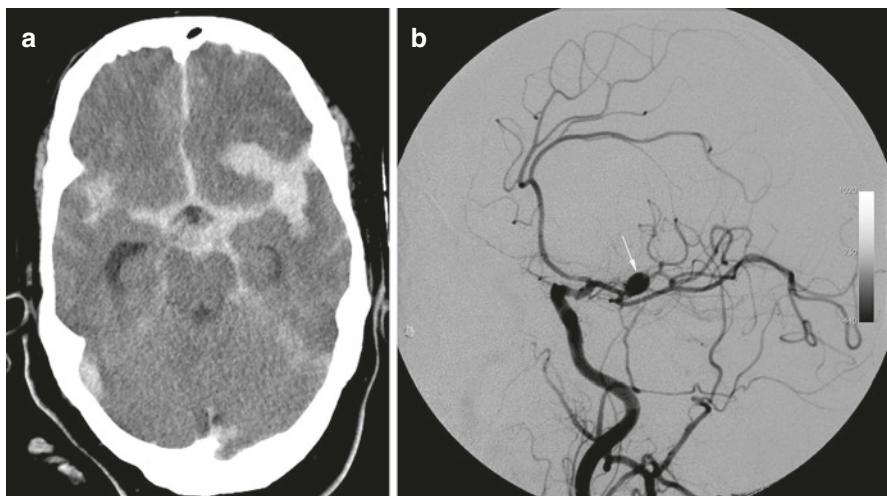
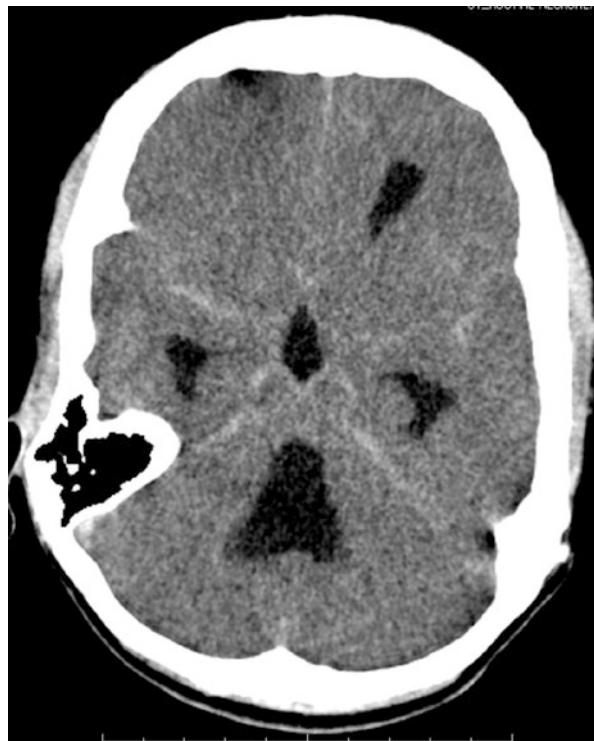


Fig. 2.10 SAH. NCCT shows (a) diffuse hyperdensity in the basal and sylvian cisterns suggestive of SAH. DSA (b) shows a left MCA bifurcation aneurysm (white arrow)

Fig. 2.11 Pseudo SAH on NCCT in a brain-dead patient. Diffuse hypodensity of brain parenchyma with loss of grey–white matter differentiation and hyperdense subarachnoid spaces mimicking diffuse SAH



longer study time and cost). It does, however, have a role to play in subacute or chronic cases, where the CT may have returned to normal [61].

Imaging of Aneurysms

Selective catheter cerebral angiography is currently the standard for determining cerebral aneurysms as the cause of SAH. Digital subtraction angiography (DSA) provides accurate assessment of the aneurysm's location, size, geometry, relationship to adjacent vessels and potential multiplicity (Fig. 2.10b). Approximately 20–25% of DSAs performed for SAH will not indicate a source of bleeding [62]. MRA and CTA may be considered when conventional angiography cannot be performed in a timely fashion [57]. The sensitivity of 3D ToF MRA for cerebral aneurysms is 85–100% for detecting >5 mm aneurysms and drops to 56% for detecting <5 mm aneurysms [63–65]. CTA is a readily available, rapid and less invasive alternative to catheter angiography. CTA is better at defining aneurysmal wall

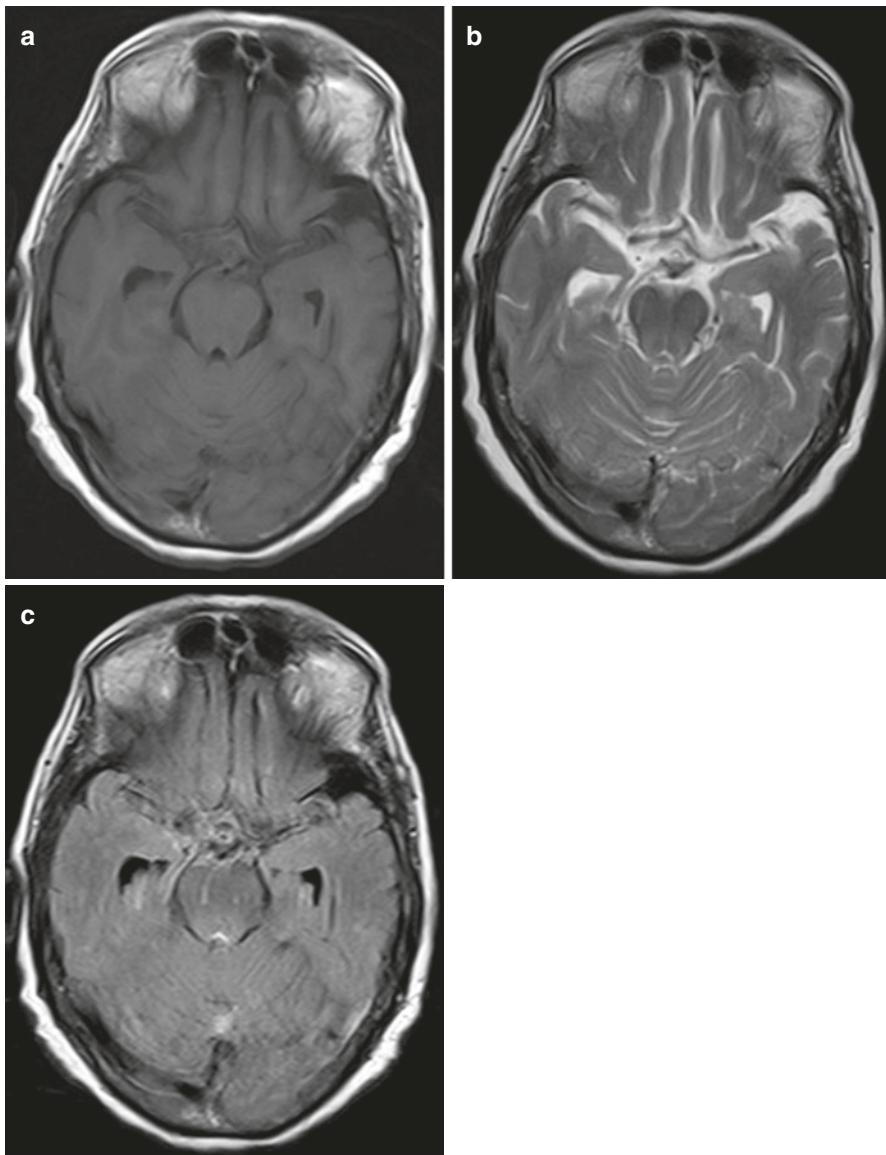


Fig. 2.12 MR in SAH. A 45-year-old man with history suggestive of SAH 3 days back. T₁- (a) and T₂-WI (b) are unremarkable. FLAIR image (c) shows hyperintensity in the basal cisterns suggesting SAH in a given clinical scenario

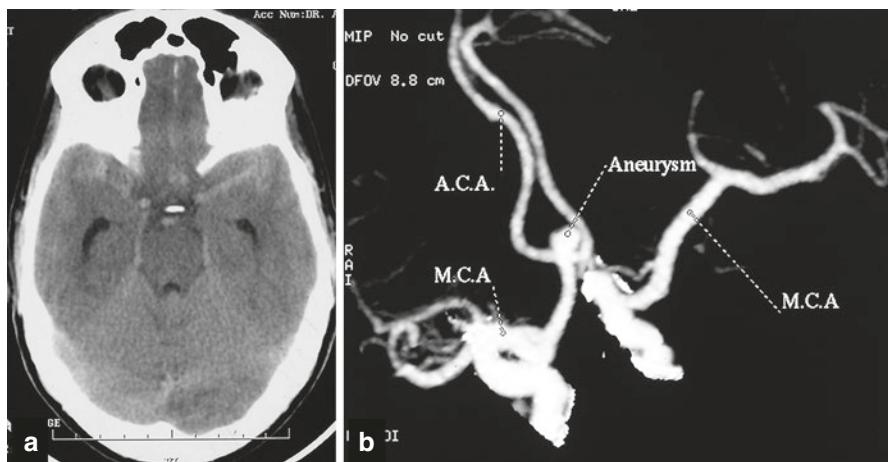


Fig. 2.13 CTA. NCCT (a) shows diffuse SAH in the basal cistern, and CT angiography (b) shows an aneurysm in the region of the anterior communicating artery

calcification, intraluminal aneurysmal thrombosis, orientation of the aneurysm with respect to intraparenchymal haemorrhage and the relationship of the aneurysm to bony landmarks. For aneurysms that are 5 mm, CTA has sensitivity of 95–100% compared with 64–83% when the aneurysms are <5 mm (Fig. 2.13) [66–68].

Cerebral Venous Thrombosis (CVT)

CVT is a relatively uncommon but serious neurological disorder. The clinical presentation is often non-specific; imaging plays a primary role in diagnosis. The imaging findings of CVT can be categorized as direct when there is visualization of a cortical or dural sinus thrombus or indirect when there are ischaemic changes related to venous outflow disturbance.

Direct Visualization of Thrombus

On NCCT, acute thrombus is seen as hyperdense area within the dural sinus (dense triangle sign) (Fig. 2.14a) or cortical vein (cord sign), which is reported in 20% of patients [69] and takes 1–2 weeks to disappear [70]. It should not be confused with hyperdensity in the venous sinuses seen in patients with dehydration, an elevated haematocrit level, or a subjacent subarachnoid or subdural haemorrhage. On contrast administration, CVT appears as a central intraluminal filling defect (empty delta sign) that represents a thrombus surrounded by contrast-enhanced dural collateral venous channels and cavernous spaces within the dural envelope (Fig. 2.14b).

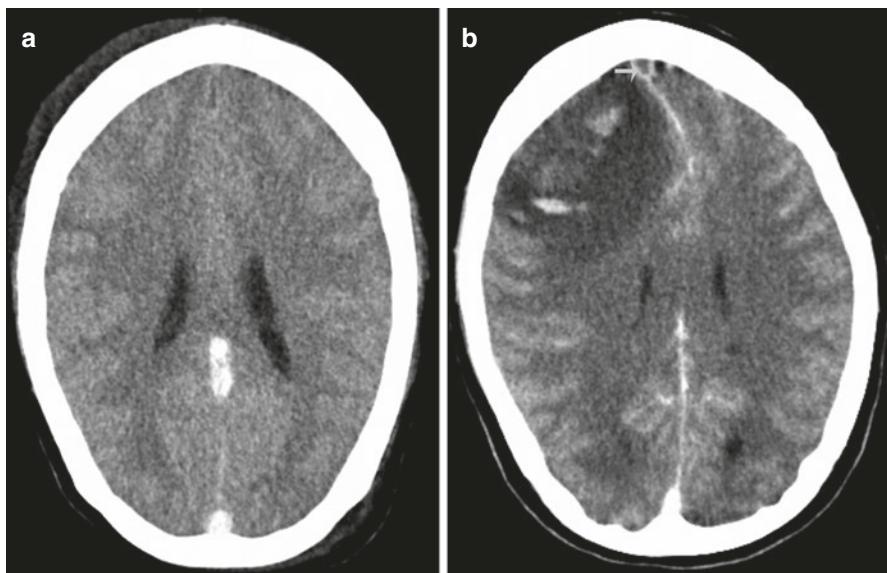


Fig. 2.14 Cerebral venous thrombosis. NCCT (a) shows a hyperdense straight sinus (white arrow) and superior sagittal sinus (black arrow) suggesting thrombosis. Another case of right frontal venous infarct in the superior sagittal sinus. CECT (b) shows a filling defect (small arrow) within the anterior superior sagittal sinus (empty delta sign)

The empty delta sign, seen in 25–75% of cases, can disappear in the chronic stages with enhancement of an organized clot [71]. In 10–30% of cases of CVT, the findings on either non-enhanced or contrast-enhanced CT are negative. Therefore, in highly suspicious cases, further evaluation with CT venography (CTV) or MRI with MR venography (MRV) is warranted.

MRI is the modality of choice in CVT [72]. Unenhanced MRI is more sensitive for the detection of venous thrombi than unenhanced CT (Fig. 2.15). The signal intensity of venous thrombi on MRI changes over time, according to the biochemical status of haemoglobin (Table 2.5). Considerable variability can exist in the appearance of each stage in different segments in a given patient and between patients in the same clinical stage [73, 74].

The most commonly used venographic techniques currently include unenhanced ToF MRV, contrast-enhanced (CE) MRV and CTV. In MRV, thrombosis is suggested by the absence of a normal flow signal in a sinus or a vein. 2D ToF MRV is the method most commonly used for the diagnosis of CVT because of its excellent sensitivity to slow flow and diminished sensitivity to signal loss from saturation effects. CE MRV better visualizes small vessels and dural sinuses, compared with ToF MRV [75].

CTV is a rapid, readily available and accurate technique for detecting CVT [76, 77]. Reported advantages of CTV compared with MRI techniques are rapid image acquisition (reduction of motion-related artefacts), no contraindication to

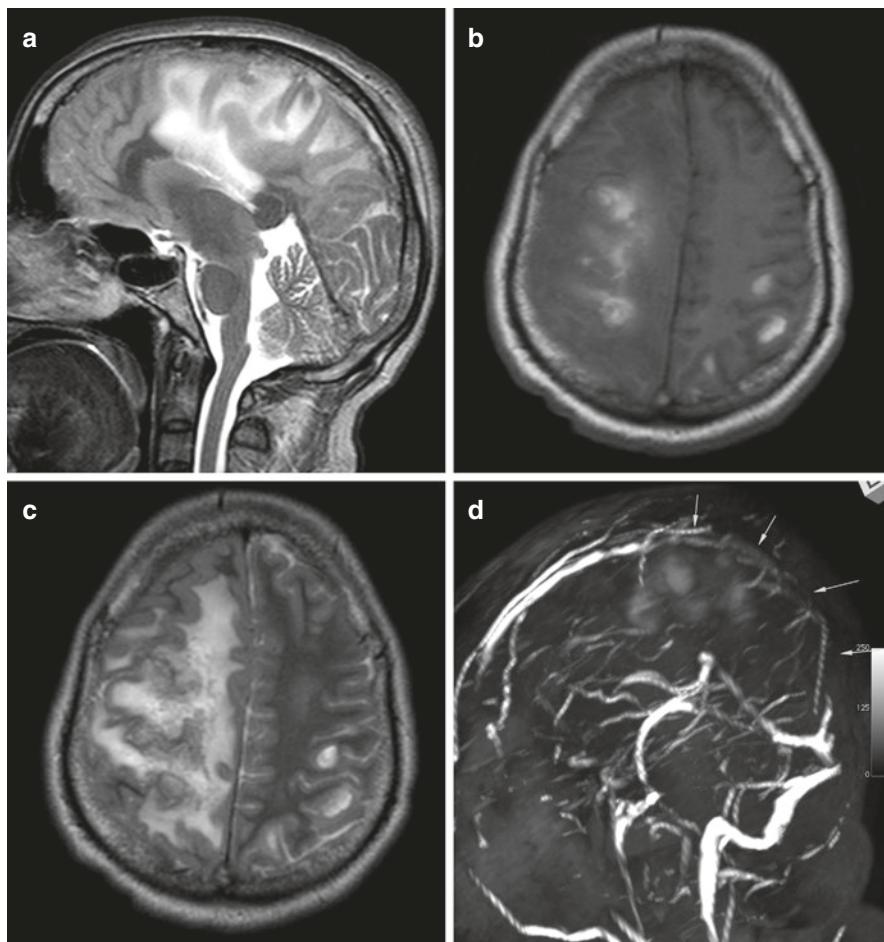


Fig. 2.15 Superior sagittal sinus thrombosis. Sagittal T₂-WI (a), axial T₁-WI (b) and axial T₂-WI (c) show loss of flow void in the superior sagittal sinus and venous infarcts in bilateral frontoparietal lobes. ToF MRV (d) shows non-visualization of the posterior superior sagittal sinus (arrows) confirming thrombosis

Table 2.5 Signal intensity of venous thrombi on MRI

Approximate stage	Clinical biochemical forms	T ₁ -weighted image	T ₂ -weighted image	Remarks
Acute thrombus	Paramagnetic deoxy-haemoglobin in RBCs	Isointense	Hypointense	May be mistakenly thought to indicate a flow void; suggest MRV or CTV
Subacute thrombus	Methaemoglobin in the thrombus	Hyperintense	Hyperintense	
Chronic thrombus	Vascularized connective tissue of chronic thrombus	Isointense	Hyperintense	

pacemaker and ferromagnetic devices and increased imaging resolution. Limitations of CTV include exposure to ionizing radiation, adverse reactions to iodinated contrast medium and limited visualization of skull base structures in 3D display.

Variations in the normal venous anatomy may mimic sinus thrombosis on CTV or MRV [78, 79]. These include venous anatomical variants that mimic occlusion (sinus atresia or hypoplasia), asymmetrical or variant sinus drainage (occipital sinuses, sinus duplication) and normal sinus filling defects (arachnoid granulations, intrasinus septa).

Cerebral catheter angiography is rarely used for the diagnosis of CVT; conventional angiography best demonstrates the dynamics of the intracranial circulation. Dilated, tortuous collateral veins develop in the setting of chronic venous hypertension related to veno-occlusive disease. This constellation of findings in the venous phase of the angiogram has been referred to as a ‘pseudophlebitic pattern’ [80].

Indirect Signs Secondary to Veno-occlusive Disease

The pathophysiology of venous stroke is not fully understood. However, several reports suggest that the venous outflow obstruction results in raised intracranial pressure (ICP), increased retrograde venous pressure, a decrease in the CBF, decreased cerebral perfusion pressure and, eventually, venous infarction [81]. Haemorrhage often accompanies the venous infarct.

Venous infarction manifests as a low-density lesion on CT scan, [81] with or without subcortical haemorrhage (Fig. 2.14b) [82]. On MRI, FLAIR and T2-WI show cortical and subcortical high-signal intensity lesions (Fig. 2.15) [83]. DWI reveals mixed signal intensity and relates to both cytotoxic and vasogenic oedema [83, 84]. In contrast to arterial infarct, a reduced ADC value in CVT may not correlate with neuronal death and a permanent neurological deficit [84]. Bilateral parasagittal hemispheric lesions are suggestive of superior sagittal sinus thrombosis (Fig. 2.15). Ipsilateral temporo-occipital and cerebellar lobe lesions can be found in transverse sinus thrombosis. Bilateral or unilateral infarction in the thalamami, basal ganglia and internal capsule is typically seen in deep venous thrombosis (Fig. 2.16). Table 2.6 depicts the difference between venous and arterial infarcts.

Infection

When intracranial infection is suspected, it is mandatory to initiate prompt and appropriate treatment to ensure a successful outcome. Although an LP can be performed in a suspected case of meningitis with no adverse neurological sign, CT should be performed (if readily available) prior to LP to exclude evidence of raised ICP, obstructive hydrocephalus or mass lesion. Different infective agents have different, and sometimes characteristic, findings on CT and MRI.

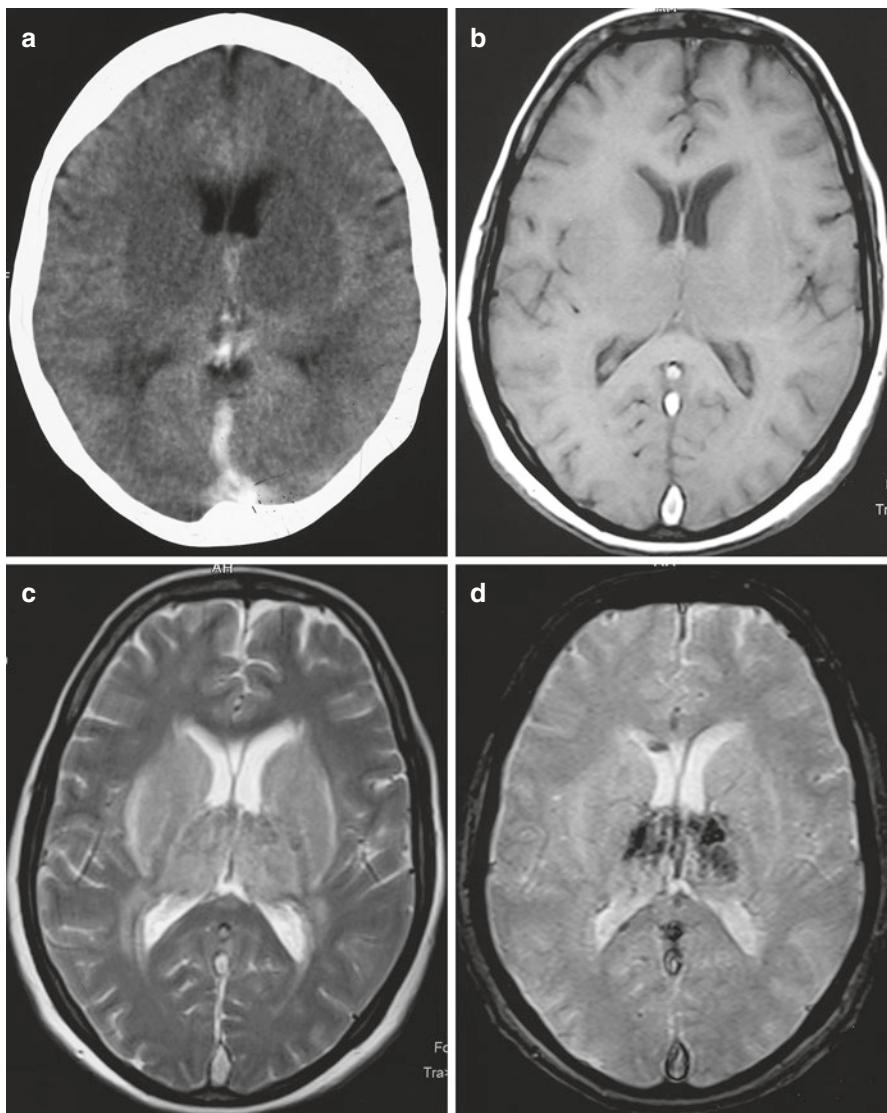


Fig. 2.16 Deep venous sinus thrombosis. Signal abnormalities are seen in bilateral basal ganglia and thalamus which appear hypointense on CT (a), hypointense on T₁-WI (b) and hyperintense on T₂-WI (c) with evidence of haemorrhage in T₂-gradient images (d). Both internal cerebral veins (short black arrows) and straight sinus (long black arrows) appear hyperintense on NCCT (a) and hyperintense on T₁- (b) and T₂-WI (c) suggesting acute thrombosis

Table 2.6 Differences between venous and arterial infarcts

	Venous infarct	Arterial infarct
Distribution	An infarction not conforming to a major arterial vascular territory but occurring as multiple isolated lesions, involving a subcortical region with sparing of the cortex and extending over more than one arterial distribution [85]	Follows vascular territories
CVT	Associated with CVT	Not associated with CVT
Edges	Irregular edges of areas of venous congestion or infarction	Sharper geometrical margins
Haemorrhagic transformation	Haemorrhage tends to spread from centre to periphery	Haemorrhage usually starts at the edges
Diffusion MRI	Variable diffusion; reduced ADC value in CVT may not correlate with neuronal death and a permanent neurological deficit [84]	Acute infarct shows restricted diffusion

CTV cerebral venous thrombosis

Meningitis and Its Complications

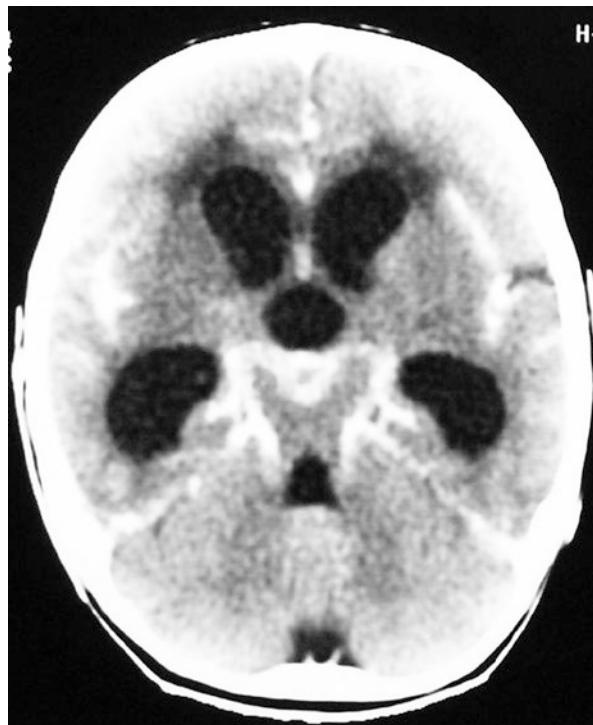
Imaging is not required for diagnosing meningitis but for identifying associated complications.

The typical radiographic finding is abnormal meningeal enhancement, usually most pronounced in the basal cisterns and better appreciated on gadolinium-enhanced MRI than on CT (Fig. 2.17). Meningeal enhancement can extend into the ambient, sylvian and prepontine cistern, around the optic chiasma and over the surface of the cerebral and cerebellar hemispheres. This appearance is non-specific and has a wide differential diagnosis that includes tuberculous meningitis, non-tuberculous bacterial meningitis, non-infectious inflammatory disease affecting the leptomeninges (e.g. sarcoidosis and rheumatoid arthritis) and neoplastic involvement of the meningeal surfaces (e.g. neoplastic meningitis from a peripheral metastatic tumour, CSF seeding of tumour from a primary CNS focus). Tuberculous meningitis may be associated with intraparenchymal tuberculomas or miliary tuberculosis [86].

Hydrocephalus is the most common complication associated with meningitis (Fig. 2.17). It is related to inflammatory debris blocking the flow and resorption of CSF, particularly at the level of the arachnoid villi [87]. An exudative obstruction may also occur within the cerebral aqueduct or along the foraminal outflow of the lateral or fourth ventricles. Occasionally, it may be of the extraluminal obstructive type due to a focal parenchymal lesion with mass effect.

Ventriculitis may be seen in direct association with meningitis, secondary to the rupture of a parenchymal abscess into the ventricular system or after ventricular

Fig. 2.17 Meningitis with hydrocephalus. Contrast-enhanced CT scan shows enhancing exudates in the basal cisterns and sylvian fissures with dilatation of the ventricles



catheter placement. On imaging, ventriculomegaly is often present, associated with abnormal increased signal intensity along the periventricular margins, well seen on FLAIR images. Marked periventricular enhancement is seen after contrast administration.

Ischaemic infarcts are also a common complication of tubercular meningitis and are seen in 20–40% of patients on CT, mostly within the basal ganglia or internal capsule regions and resulting from either secondary extension of the arachnoiditis to the vessels or direct vessel invasion [87–89].

Cerebritis and Abscess

Brain abscess can be a lethal condition if appropriate treatment is delayed. A brain abscess results from direct spread of infection, either an otorhinological infection or meningitis (including retrograde septic thrombophlebitis), or from haematogenous spread from an extracranial source of infection.

Pyogenic abscesses evolve through the early cerebritis, late cerebritis, early capsular and late capsular stages of formation. The imaging appearance of abscesses depends on the stage of the lesion. In the cerebritis stage, pyogenic abscesses are

seen as hypointense areas on CT; T₁-hypointense and T₂-hyperintense areas are seen on MRI with minimal or non-homogeneous enhancement following contrast administration. Mature pyogenic abscess is characterized by the formation of a distinct collagenous capsule that is iso-hyperdense on CT (Fig. 2.18), isointense on T₁-WI and hypointense on T₂-WI (Fig. 2.19). The capsule of an abscess enhances strongly, uniformly and continuously following contrast administration (Figs. 2.18 and 2.19). The cavity of the mature abscess shows low T₁ and high T₂ signal with low ADC on DWI, suggesting restricted diffusion within the core of the abscess (Fig. 2.19) [90, 91]. Table 2.7 shows the differentiating features between pyogenic, tubercular and fungal brain abscesses.

The differential diagnosis for a ring-enhancing lesion includes a primary brain tumour (high-grade astrocytoma), metastasis, infarction (bland or septic), resolving haematoma, thrombosed aneurysm, radiation necrosis, AIDS-related lymphoma and other inflammatory conditions (e.g. demyelinating disease, granulomata, etc.).

DWI MRI is helpful in differentiating an abscess from a necrotic tumour. On DWI, an untreated abscess cavity demonstrates high-signal intensity with a corresponding low ADC. In contrast, tumours with central necrosis have an appearance of marked hypointensity on DWI images and much higher ADC values. Magnetic

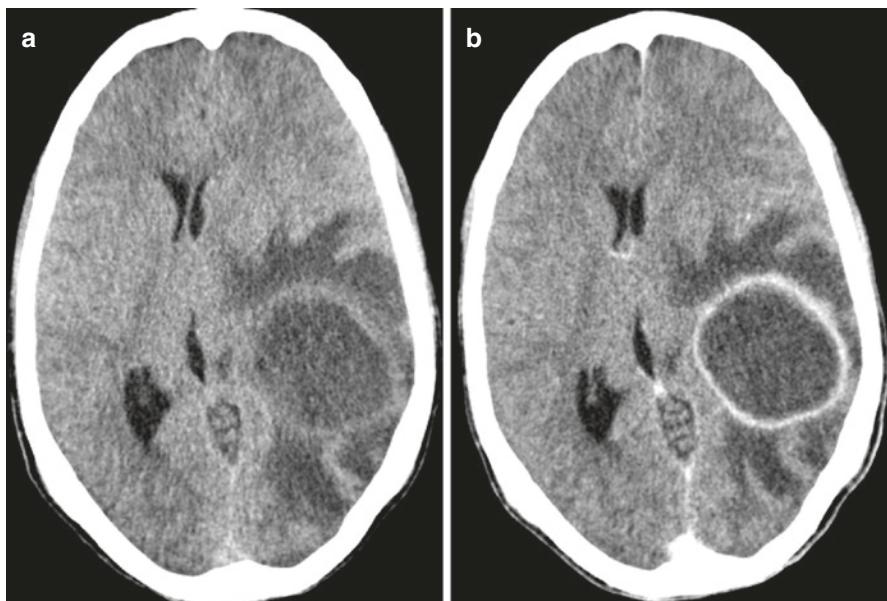


Fig. 2.18 Brain abscess. NCCT (a) shows a ring lesion with an isodense wall and hypodense centre in the left temporo-parietal region. Following intravenous contrast administration, there is smooth, uniform enhancement of the abscess capsule (b)

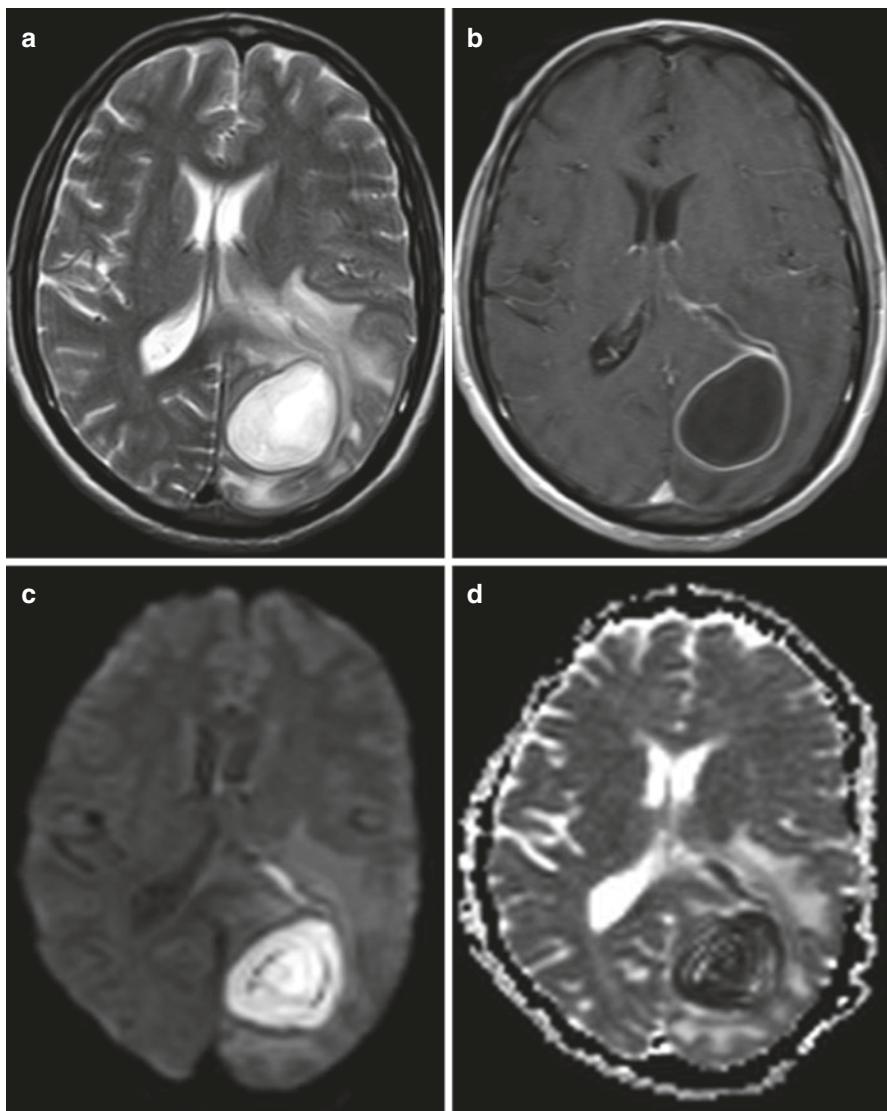


Fig. 2.19 Left occipital lobe abscess. The abscess has a hypointense rim on T₂-WI (a) and shows smooth ring enhancement following gadolinium administration (b). The core of the abscess is bright on DWI (c) and hypointense on ADC (d), suggesting restricted diffusion

resonance spectroscopy (MRS) is another useful tool to differentiate these two conditions. Acetate, succinate and amino acid peaks may be present in abscesses but not in necrotic/cystic tumours. The central portion of a necrotic/cystic tumour often reveals only a lactate resonance peak.

Table 2.7 Differences between pyogenic, tubercular and fungal brain abscesses on MRI

	Conventional MR	Contrast-enhanced MR	Diffusion MR
Pyogenic abscesses	Smooth and lobulated walls with no intracavitory projections	Ring enhancement usually thin, smooth and often thinner along medial margin	Wall and cavity show low ADC (hyperintense on DWI image) [92, 93]
Tuberculous abscesses	Smooth, lobulated or crenated walls with no intracavitory projections, frequently multiloculated and larger [86]	Ring enhancement usually thin, smooth and often thinner along medial margin	Wall as well as cavity show low ADC (hyperintense on DWI image)
Fungal abscesses	Irregular walls (lobulated/crenated) with non-enhancing irregular intracavitory projections into core of abscess [94]	Ring enhancement usually thin, smooth and often thinner along medial margin	Wall and projections show low ADC (hyperintense on DWI image); however, the cavity itself shows high ADC (hypointense on DWI image) [94]

Encephalitis

Herpes Simplex Encephalitis (HSE)

Herpes simplex viral encephalitis in children and adults is the most frequent nonendemic cause of acute necrotizing encephalitis. Untreated HSE has an extremely high mortality rate, and early diagnosis is essential, as the prognosis depends on early recognition.

In adults, HSE typically involves the anterior and medial aspects of the temporal and the orbitofrontal regions bilaterally but is asymmetrical in distribution. The insular, angular and posterior occipital cortices to the higher frontal and parietal cortices may also be involved [95, 96]. In up to 55% of patients, extratemporal involvement occurs in the frontal, parietal and occipital lobes, limbic system, cingulate gyrus, brainstem and thalamus [95, 97]. Pure extratemporal involvement occurs in 15% of patients with HSE [95].

MRI, especially when combined with DWI, is more sensitive than CT in detecting early brain changes in HSE [98–100]. Initial CT scan is normal in up to 25% of HSE patients and becomes positive only after week 2 [95, 101]. Occasionally, subsequent CT shows hypodense areas with mass effect localized to the temporal lobe, which can progress to radiolucent or haemorrhagic lesions involving both temporal lobes, particularly late in the course of the disease [101].

On MR examination, lesions are usually isointense or hypointense on T₁-WI and hyperintense on T₂-WI or FLAIR images (Fig. 2.20). On DWI, in the early stage of the disease, cytotoxic oedema causes a decrease in water diffusion, as well as an increase in diffusion on account of vasogenic oedema (Fig. 2.20). These two early changes usually take place concurrently in most patients and seldom occur

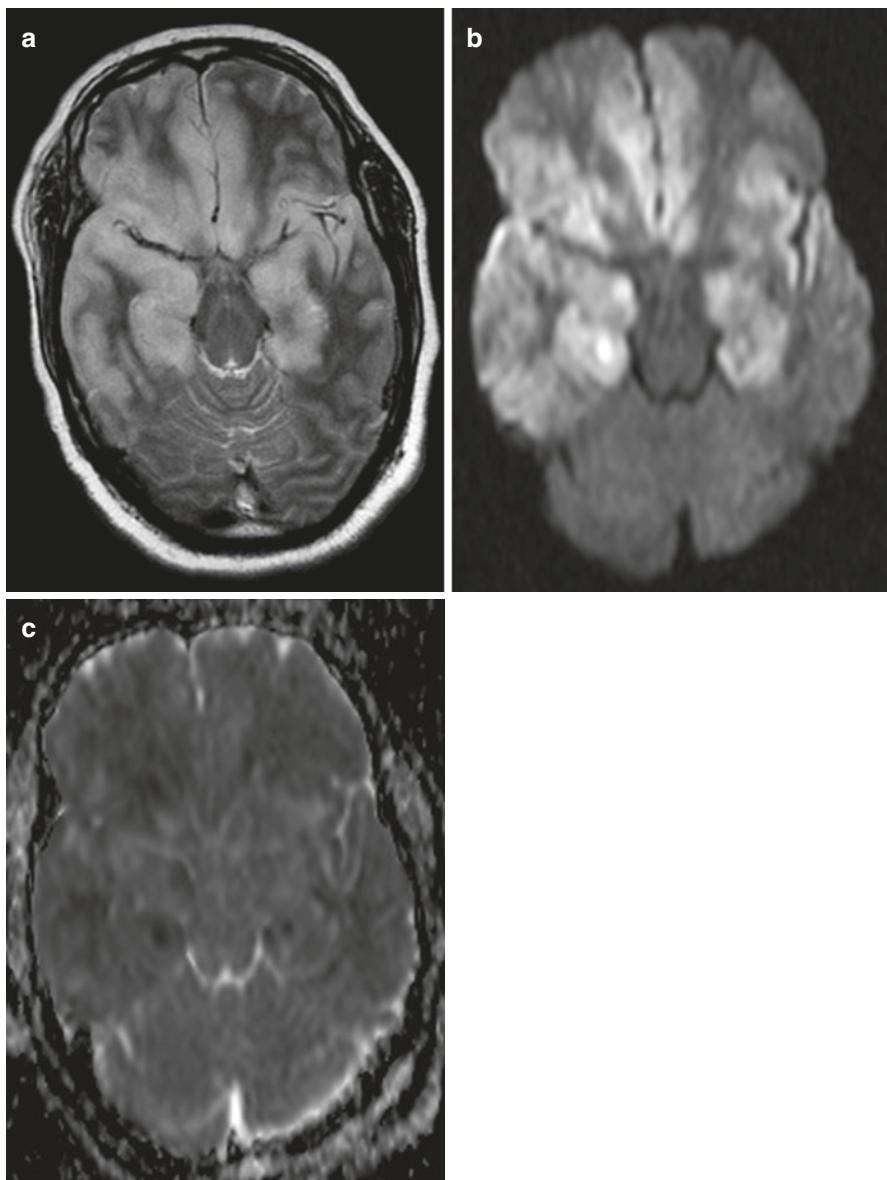


Fig. 2.20 Herpes encephalitis. Lesions involving the bilateral temporal lobes including hippocampi, basifrontal regions show cortical thickening and high-signal intensity on T₂-WI (a). Lesions show evidence of restricted diffusion on DWI (b) images and ADC maps (c)

individually. Different enhancement patterns, such as gyral, meningeal, diffuse or ringlike, have been reported in up to 50% of patients following initiation of T₂ signal abnormality [95].

Arbovirus Infections

Flaviviridae are a prominent group of arboviruses that include agents causing Japanese, West Nile, St Louis and Murray Valley encephalitides—all of which belong to the Japanese encephalitis (JE) antigenic complex, as well as tick-borne encephalitides.

Japanese Encephalitis (JE)

JE is a major health problem in Asia and commonly presents as acute viral encephalitis or meningoencephalitis.

MRI is more sensitive than CT in revealing the characteristic radiological changes of JE [102]. The characteristic imaging findings of JE include bilateral thalamic and brainstem lesions, especially the substantia nigra, which are of low attenuation on CT and of high T₂ signal on MRI (Fig. 2.21). The cerebellum, cerebral cortex and basal ganglia may also be affected. The abnormalities are frequently haemorrhagic, and bilateral thalamic haemorrhages are considered highly specific for JE. Medial temporal lobe involvement may also be encountered, characteristically in the posterior part of the hippocampus. Unlike in HSE, the anterior temporal lobe is usually spared and insular involvement is rare [103]. DWI is helpful in establishing an early diagnosis of JE by showing the characteristic involvement of the bilateral thalami at an early stage [104].

The imaging findings of encephalitides caused by other *Flaviviridae* are similar to those of JE. West Nile virus encephalitis may show some additional findings or present with normal imaging studies. Isolated abnormalities on DWI can be detected in the cerebral white matter in milder cases. In patients with flaccid paralysis, abnormal high T₂ signal in the ventral grey matter horns and/or enhancement around the *conus medullaris* and *cauda equina* is found on MRI [105].

Enteroviruses

The enteroviruses include Coxsackie viruses A and B, poliovirus, echoviruses and enteroviruses [75–78] and may cause a number of disease processes, including poliomyelitis, meningitis and encephalitis. Pathological CNS involvement by enteroviruses is characteristically located in the dorsal medulla oblongata, dorsal pons, central portion of the midbrain, bilateral dentate nuclei of the cerebellum and ventral horns of the cervical spinal cord [106]. MRI studies accordingly show high

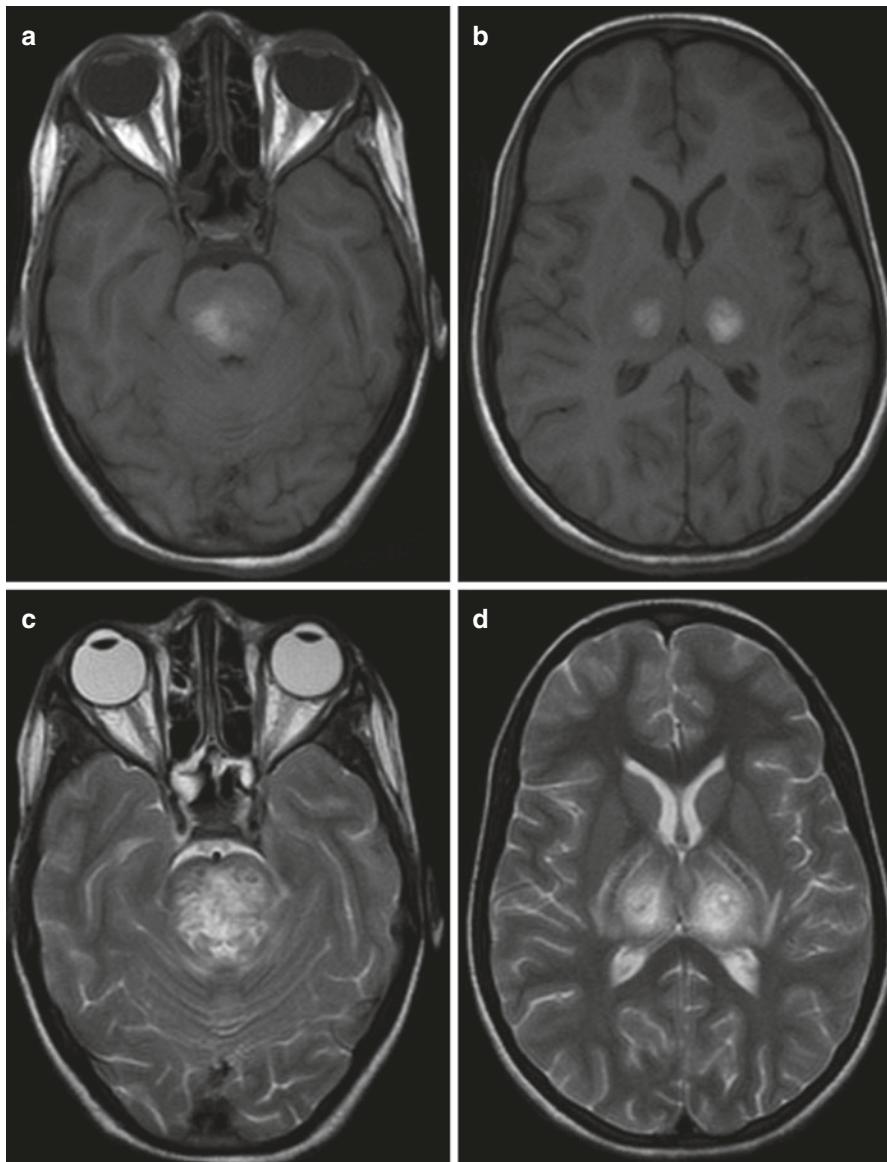


Fig. 2.21 Japanese encephalitis. Lesions involving the pons and bilateral thalami show central T₁ hyperintensity (a and b) with surrounding hypointensity suggesting haemorrhage and T₂ hyperintensity (c and d)

T_2 signal in the involved areas with symmetrical bilateral lesions in the dorsal brain-stem and ventral horns of the cervical spinal cord. These findings are considered characteristic of enteroviral encephalomyelitis [107].

Demyelinating Disease

Acute Disseminated Encephalomyelitis (ADEM)

ADEM is a monophasic, demyelinating disease of the CNS typically affecting the grey and white matter of the brain and spinal cord at multiple locations.

Conventional MRI findings characteristically include multiple, poorly marginated, hyperintense areas on T_2 -WI and FLAIR images in the deep and subcortical white matter of the cerebral hemispheres, deep grey matter nuclei (i.e. thalamus and basal ganglia), cerebellar white matter and brain stem (Fig. 2.22). The cerebral cortex is involved in ~30% of cases, and occasionally, selective involvement of the cerebral cortex may be the only manifestation of ADEM, although it would be a diagnosis of exclusion. The white matter lesions are typically distributed asymmetrically and deep grey matter nuclei lesions often have a symmetrical appearance. Mass effect often is negligible. Nodular, patchy or gyriform enhancement may be seen during the acute stage of demyelination (Fig. 2.22).

The spinal cord, involved in 30% of patients, [108] may show multiple, more or less well-defined T_2 hyperintense areas within the cord. DWI shows variable findings, depending on the stage of the disease, with restricted diffusion in the acute stage (i.e. within 7 days of clinical onset) [109] and increased diffusion in the subacute stage (i.e. after 7 days of the onset) [109]. Restricted diffusion does not seem to imply irreversible damage in ADEM.

Multiple sclerosis (MS) and ADEM may be difficult to distinguish; however, some imaging features might help (Table 2.8).

Toxic Encephalopathy

Wernicke Encephalopathy (WE)

WE is an acute neurological disorder that results from thiamine (vitamin B₁) deficiency. The disease is characterized by changes in consciousness, ocular dysfunction and gait disturbances. MRI typically shows highly symmetrical T_2 and FLAIR signal in the medial thalami, mammillary bodies, tectal plate and the periaqueductal area [110–112]. Typical MRI findings include signal intensity alterations in the cerebellum, cerebellar vermis, cranial nerve nuclei, red nuclei, dentate nuclei, caudate

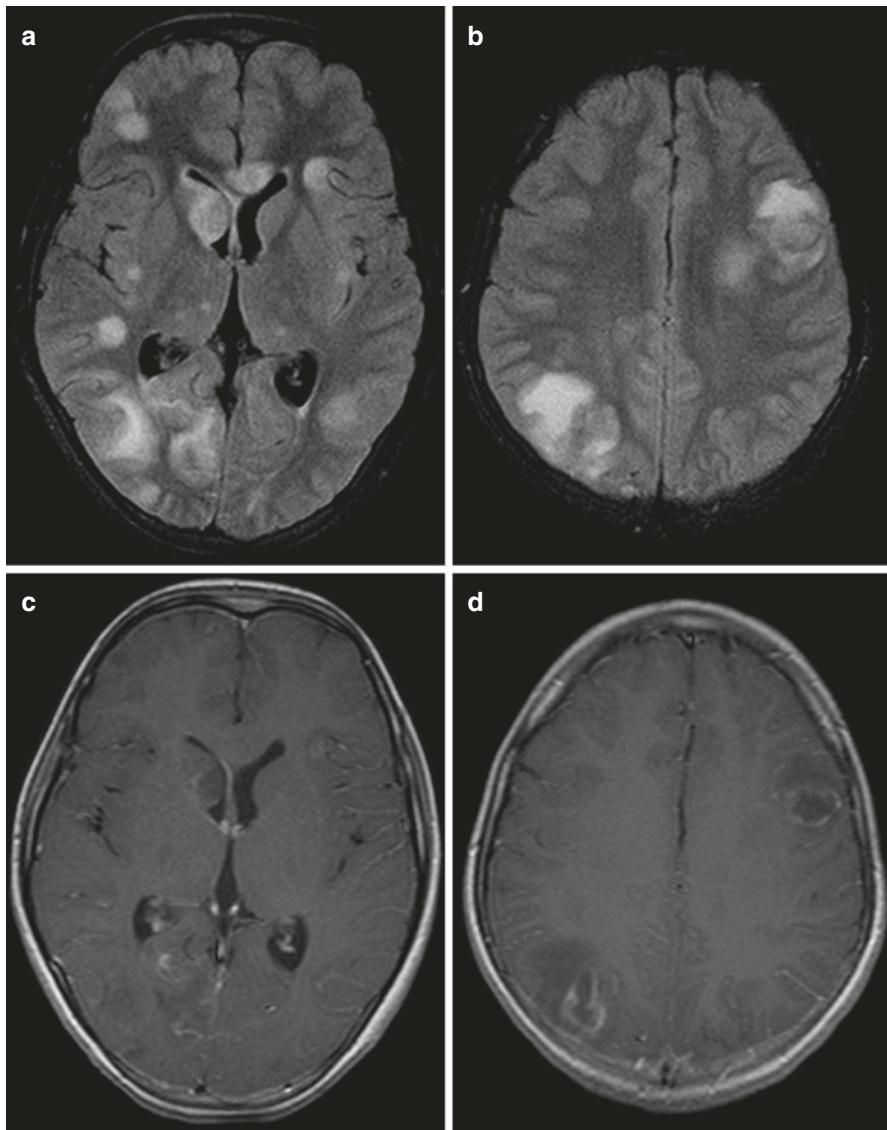


Fig. 2.22 ADEM. Axial FLAIR (a and b) images show multifocal lesions in both cerebral hemispheres and deep grey matter nuclei, which shows curvilinear/ring or no enhancement following gadolinium administration (c and d)

nuclei, splenium and cerebral cortex [110, 113]. Rarely, contrast enhancement of the mammillary bodies may be the only sign of WE [110]. Typical MR findings of WE occur in patients with alcoholism, [114] whereas atypical MRI findings of WE occur in non-alcoholic patients only [112].

Table 2.8 Classical features of acute disseminated encephalomyelitis (ADEM) compared with relapsing multiple sclerosis (MS)

	ADEM	Relapsing MS
Clinical course	Typically monophasic	Classically has periods of exacerbations and remissions
Myelopathy	Often complete and associated with areflexia	Partial
MR brain	Multifocal, large lesions, may involve brainstem Cortical grey matter, thalamic and basal ganglia lesions more common in ADEM than in MS and often show some symmetry Often (but not strictly) synchronous enhancement (lesions of similar age initially)	Brain with multifocal lesions Periventricular lesions more common than in ADEM Chronic T ₁ hypointensities (black holes) Only acute lesions may show enhancement
MR spine	May have long vertical involvement greater than that for MS Typically has complete transverse involvement May have prominent cord swelling	Vertically oriented but length ≤2 vertebrae Typically has partial transverse involvement Mild swellings only in the acute stage

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES, also known as reversible posterior encephalopathy syndrome, is a syndrome characterized by headache, confusion, seizures and visual loss. It may have a number of causes, predominantly malignant hypertension, eclampsia and drugs, such as tacrolimus and cyclosporine in the post-transplant setting.

On CT or MRI, focal regions of symmetrical, hemispherical high T₂ signal are typically present in the occipital and parietal regions but also in the frontal lobes (in particular, along the superior frontal sulcus), inferior temporo-occipital junction and cerebellar hemispheres (Fig. 2.23) [115–117]. The brain stem, basal ganglia, deep white matter (external/internal capsule) and splenium may also be involved. The regions of involvement characteristically show vasogenic oedema with increased diffusion; areas of restricted diffusion are uncommon (11–26%) and may be associated with an adverse outcome [118, 119]. Haemorrhage (focal haematoma, isolated sulcal/subarachnoid blood or protein) is seen in ~15% of patients [120, 121].

Catheter angiography, MRA and MR perfusion demonstrate evidence of vasculopathy with focal and diffuse vasoconstriction, focal vasodilation and a string-of-bead pattern, along with reduced regional CBV (rCBV) suggesting a state of brain hypoperfusion [115].

Hepatic Encephalopathy

The most common clinical pattern in patients with hepatic encephalopathy is the development of confusion or coma precipitated by gastrointestinal bleeding, acute superimposed hepatitis or concomitant infection in a previously asymptomatic patient with cirrhosis.

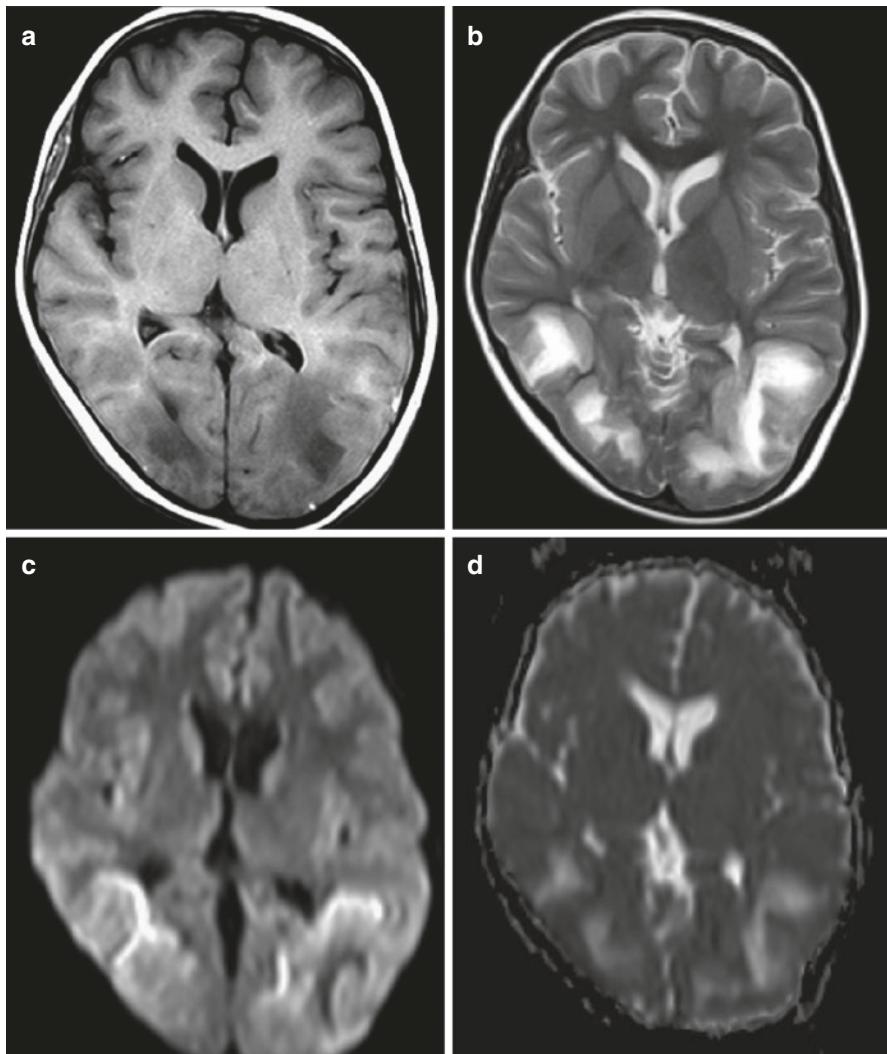


Fig. 2.23 Posterior reversible leucoencephalopathy. Signal abnormalities are seen bilaterally in the parieto-occipital region. These appear isohyperintense on T₁-WI (a) and hyperintense on T₂-WI (b) and show a mixed pattern of restricted and increased diffusion on DWI (c) and ADC maps (d)

Conventional MRI may reveal a bilateral, symmetrical, high T₁ signal intensity of the globus pallidus and substantia nigra caused by increased brain tissue concentration of manganese [122, 123], diffuse white matter, high T₂ and FLAIR signal intensities involving predominantly the hemispheric corticospinal tract and focal high T₂ signal lesion in the subcortical hemispheric white matter. All these MRI abnormalities return to normal with restoration of liver function.

Hypoglycaemic Encephalopathy

Hypoglycaemia may be caused by overuse of insulin or oral hypoglycaemic agents, an undiagnosed insulinoma, or major medical illnesses such as sepsis, renal or hepatic failure or Addison disease. Lesions involve the temporal, occipital and insular cortices, the hippocampus and the basal ganglia and middle cerebellar peduncles, with sparing of the thalamus [124]. Additionally, the deep white matter may be involved, with hypoglycaemic injury in the form of symmetrical hyperintensity involving the internal capsule, corona radiata and splenium on T₂-WI. The lesions may show restricted diffusion [125].

Osmotic Pontine and Extrapontine Myelinolysis

Osmotic pontine myelinolysis commonly affects patients with chronic alcoholism and those with an electrolyte imbalance. Symptoms include tetraplegia, pseudobulbar palsy and acute changes in mental status leading to coma or death without intervention.

Conventional MRI findings may lag behind the clinical manifestation of central pontine myelinolysis. The classic appearance is a trident- or triangle-shaped central pontine high T₂ and low T₁ signal intensity without enhancement or mass effect (Fig. 2.24a) [126, 127]. In more severe disease, almost the entire central pons may be involved with only a thin rim of normal signal around it.

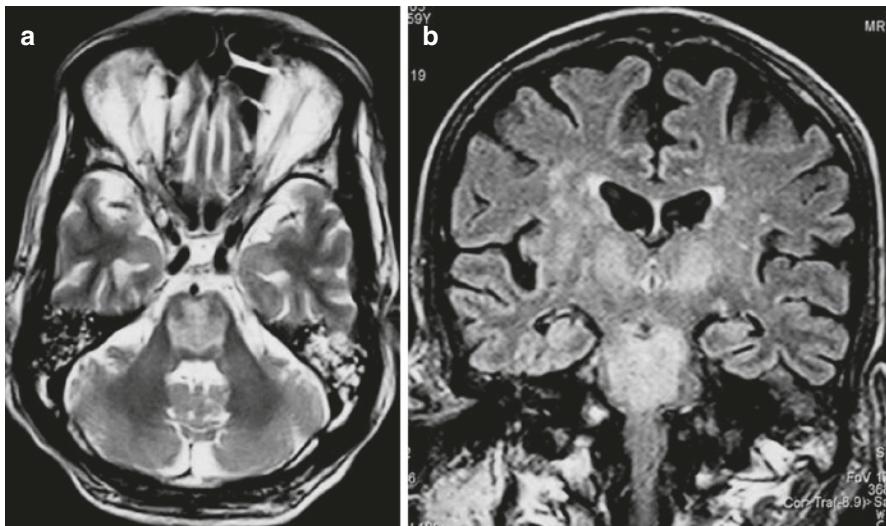


Fig. 2.24 Pontine and extrapontine myelinolysis. Axial T₂-WI (a) and coronal FLAIR (b) images show hyperintense signal changes in the central pons and bilateral basal ganglia

Similar histologically symmetrical lesions in extrapontine locations, including the white matter of the cerebellum, thalamus, globus pallidus, putamen and lateral geniculate body, have been described and are termed ‘extrapontine myelinolysis’ (Fig. 2.24b) [128]. DWI has been shown to be useful in the early diagnosis of central pontine myelinolysis [129]. In the acute phase, DWI shows restricted diffusion suggesting the presence of cytotoxic oedema. Follow-up imaging may show recovered ADC values, suggesting the disappearance of cytotoxic oedema in the later phase.

Acute Carbon Monoxide (CO) Poisoning

CO is a colourless and odourless gas which is the most common cause of accidental poisoning in Europe and North America, as well as being a major cause of suicidal deaths. Necrosis of the globus pallidus is the most common brain injury occurring in CO poisoning. CT usually shows symmetrical hypodensity. On MRI, the medial portions of the globus pallidus appear as bilateral areas of low T₁ signal and high T₂ signal. DWI and ADC maps show restricted diffusion caused by cytotoxic oedema from acute tissue necrosis [130]. The caudate nucleus, putamen and thalamus are occasionally involved in CO poisoning but less so than the globus pallidus [131].

Methanol Toxicity

Methanol intoxication appears after accidental or suicidal oral ingestion of industrial solvents or cleaning and antifreeze liquids or occasionally results from fraudulent adulteration of alcoholic beverages. Bilateral putaminal necrosis, with or without haemorrhage, and subcortical white matter lesions are the most common findings [132, 133]. Additional involvement of other basal ganglia nuclei, brain stem tegmentum and cerebellum can also be seen [134]. The lesions show high T₂ and variable T₁ signal intensity, depending on the presence and stage of haemorrhage (Fig. 2.25). Enhancement is variable, ranging from none to intense. In the chronic setting, cystic cavities may develop in the putamen.

Conclusion

CT has been the traditional first-line imaging modality for the investigation of most patients presenting to the emergency department because of its widespread availability, ease and speed of use, low cost and non-invasiveness. It can accurately detect haemorrhage, mass lesions, signs of raised ICP, cerebral oedema and brain herniations. MRI is, however, becoming increasingly available. In situations in which there is a diagnostic dilemma, appropriate imaging with MRI can substantiate the clinical diagnosis and also improve the diagnostic yield, especially when the suspected clinical diagnosis is encephalitis, PRES or venous thrombosis. In these

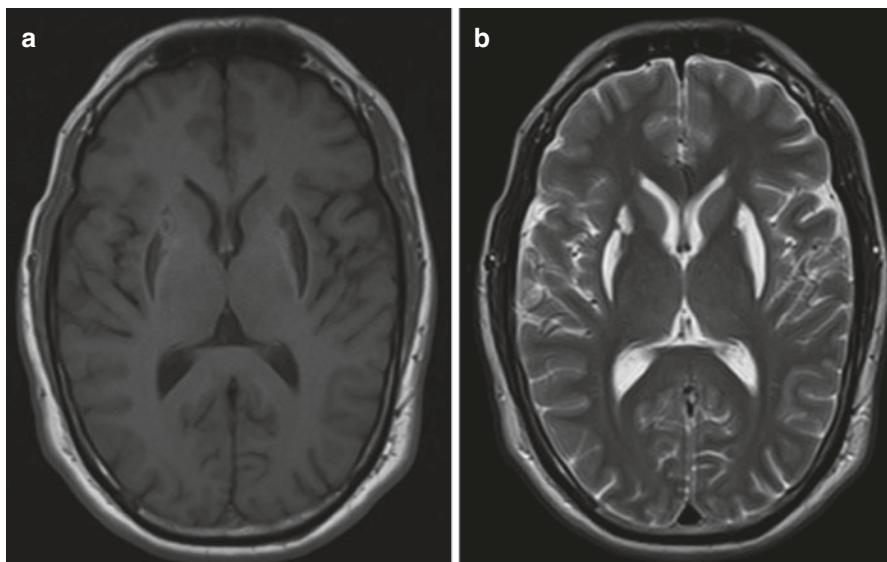


Fig. 2.25 Methanol toxicity. Bilateral putamina (white arrows) show evidence of cavitations on T₁- (a) and T₂-WI (b)

situations, MRI is the most sensitive investigation and may be performed in the first instance, provided there is immediate availability and no contraindication to MRI and the patient is cooperative. CTP techniques and DWI–PWI MRI will play important roles in the assessment of patients who have had a confirmed diagnosis of ischaemic stroke when thrombolysis treatment is being considered. Physicians should remain cognizant of the strengths and limitations of both tests.

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CSF and EEG in Neurological Emergency

3

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CSF in the Neurology Emergency

Performing a lumbar puncture and examining the cerebrospinal fluid (CSF) provides a unique opportunity to explore the internal milieu in which the brain and spinal cord are bathed. Analysis of the CSF is the cornerstone of diagnosis and management of many neurological emergencies. It also plays an important role in the diagnosis and sometimes prognostication of non-infectious diseases. Evaluation of the CSF is critical in establishing a diagnosis of infectious meningitis and in guiding antimicrobial therapy. Less commonly, a lumbar puncture (LP) is used as a part of the diagnostic workup of patients with suspected subarachnoid haemorrhage, demyelinating disease and leptomeningeal metastasis (LM) [1], all of which may present as neurological emergencies. The two major issues that may interfere with appropriate and timely CSF analysis (either by LP or shunt tap) are concerns about uncal or cerebellar tonsillar herniation and the need to initiate empirical antibiotics emergently [2]. Once the clinical indication for CSF analysis is understood, the amount to be tapped, investigations to be sent and an algorithm of action to be taken should be clearly drawn by the clinician. Doing an LP without a clear-cut question in mind is likely to cause a delay in sending samples for the most appropriate investigations.

On the other hand, repeat CSF analysis may sometimes be necessary following an urgent examination, if odd features like malignant cells (in cases of carcinomatous meningitis) [3], fungal or protozoal organisms need to be looked for specifically.

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Indications

The indications for performing a CSF examination may be many, but here the list is restricted to include only those that are emergent. They can be further classified according to the aetiology and whether they are absolute or relative (Table 3.1).

Contraindications

Whereas a CSF examination is an emergency procedure, it is pertinent to know when to defer it and do preliminary imaging studies (CT/MRI) and also when the examination could be potentially hazardous (Table 3.2).

Contraindications to performing an LP include the following:

1. A complete spinal subarachnoid block, which can result in deterioration after the LP [1].
2. Coagulation defects and patients on anticoagulation therapy, which result in an undefined level of increased risk for epidural haemorrhage. The platelet count should be >50,000, and the international normalized ratio (INR) <1.5 [6] before an LP is performed.
3. Suppuration or eroded skin at the puncture site and bacteraemia, which may result in meningitis from the LP.
4. The patient's refusal to consent for the procedure.

Table 3.1 Indications for performing a CSF examination

Diagnosis	Comment
Infectious meningitis or encephalitis	Specific tests may be sent for bacterial, viral, tubercular, fungal, amoebic causes, syphilis, Lyme disease, etc., according to suspected aetiology and endemicity
Aseptic meningitis	Apart from viral meningitis, other possibilities would include Mollaret meningitis, neurosarcoidosis and chemical meningitis
Subarachnoid haemorrhage	LP is indicated only when the CT scan is not diagnostic (or is not available)
Demyelinating disease	May not be an emergency unless ADEM is a clinical possibility
Acute inflammatory polyneuropathies	LP may be helpful only after 1 week
Leptomeningeal metastasis	May masquerade as chronic/subacute/atypical meningitis
Systemic lupus erythematosus	May present with varied neurological presentations and an infective aetiology has to be excluded
Acute metabolic encephalopathy	Only when the diagnosis is in doubt and an alternative diagnosis has to be ruled out

Table 3.2 Indications for performing cranial imaging before doing a lumbar puncture [4, 5]

Papilloedema
Focal neurological deficits
New-onset seizure (within the past 7 days)
Signs or symptoms of a lesion in the posterior fossa
Bradycardia or irregular respiration
Age >60 years
Gaze palsy
Abnormal visual fields
Facial palsy
Arm or leg drift
Abnormal language
Head trauma
Abnormal level of consciousness

Table 3.3 Safe recommended CSF volume to be removed for different age groups

	Mean CSF production (mL/h)	CSF volume (mL)	Safe CSF volume tapped (mL)
Adult	22	150–170	15–17
Adolescent	18	120–170	12–17
Young child	12	100–150	10–15
Infant	10	60–90	6–9
Term neonate	1	20–40	2–4

How Much CSF Should Be Taken Out?

It is always wise to take out an adequate amount of CSF sample and preserve some for a later test. It is important to remember that CSF tapping is fraught with practical difficulties such as scanty flow, dry tap and trauma. All these can pose serious procedural problems and at least one person who has significant experience and confidence in performing the procedure should always be at hand even if a junior member of the team may be actually doing it. Table 3.3 shows the safe limits of the volume of CSF that can be tapped [7, 8]. If an infective aetiology is suspected, four tubes of CSF, each containing ~1–2 mL of fluid, should be obtained. Typically, tubes 1 and 4 are sent for cell count and differential, tube 2 for protein and glucose and tube 3 for Gram stain and culture [9]. In children and adults, the normal CSF WBC count is in the range of 0–5 mononuclear cells (lymphocytes and monocytes). If the total WBC count is <5, the presence of a single polymorphonuclear leucocyte may be considered normal [10–12].

What if the LP Is Traumatic?

- When the LP has been traumatic, CSF protein concentration will be increased by 1 mg/dL for every 1000 RBC/mm³ [11, 12].
- To determine the true number of WBCs in the CSF, one WBC/mm³ for every 700 RBC/mm³ is subtracted from the total WBC count [13].

3. The Venereal Disease Research Laboratory (VDRL) test for syphilis and the polymerase chain reaction (PCR) test for herpes simplex virus (HSV) and Epstein-Barr virus (EBV) should be interpreted cautiously when the LP has been traumatic. When the CSF is contaminated with blood, the VDRL and CSF PCR for EBV DNA may be false-positive.
4. A false-negative HSV CSF PCR may occur when the CSF specimen contains erythrocytes or their haemolysed products [14]. Also, cryptococcal antigen may be detected in a traumatic tap in the absence of cryptococcal meningitis.

What Can One Find and What Does It Mean?

Every neurological emergency should have a tentative list of CSF tests to be performed for a suspected clinical diagnosis.

CSF Diagnostic Tests for Meningitis and Meningoencephalitis

- Cell count with differential type and protein and glucose concentrations are the basic CSF investigations, which facilitate quick decisions (Table 3.4) [15, 16].
- Gram stain and bacterial culture.
- Latex agglutination for antigens of *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Escherichia coli* K1 strains, *Haemophilus influenzae* type b and group B *Streptococcus*.
- India ink and fungal culture.
- Viral culture (for enteroviruses).
- Cryptococcal polysaccharide antigen.
- *Histoplasma* polysaccharide antigen.
- PCR for HSV1 and 2 DNA, West Nile virus, EBV, varicella zoster virus (VZV) DNA, cytomegalovirus (CMV), reverse transcriptase (RT)-PCR for enteroviruses, HIV 1 RNA.
- ELISA for IgM antibodies in HSV, VZV, Japanese encephalitis, *Mycoplasma pneumoniae*, VDRL, FTA-ABS (fluorescent treponemal antibody adsorption test) for syphilis.

Table 3.4 Comparison of CSF findings in meningitis

	Acute bacterial meningitis (ABM)	Viral meningitis/meningoencephalitis	Chronic meningitis	Normal CSF
Colour	Turbid/cloudy/purulent	Clear	Clear/ cloudy	Clear
Opening pressure (mmH ₂ O)	>180	>180	>180	180 (upper limit)
WBC count (cells/mm ³)	1000–10,000	5–1000	25–500	0–5 (0–30 in newborns)
Neutrophils (%)	>60	<20	<50	0–15
Protein (g/L)	>0.5	<1.0	>0.5	0.15–0.5
Glucose (mM)	<2.5	2.5–4.5	<2.5	2.5–4.5
CSF/blood glucose ratio	<0.3	>0.5	<0.5	0.6

- Acid-fast smear and culture for *Mycobacterium tuberculosis* and other atypical mycobacteria.
- *Borrelia burgdorferi* antibodies in endemic regions.
- Phase-contrast microscopy under wet mount for demonstrating infectious agents such as amoebae.
- Cysticercosis, toxoplasmosis and rickettsial diseases produce an eosinophilic pleocytosis in the CSF.

Special care has to be taken while dealing with a post-transplant patient presenting with a new-onset fever and altered mental status or a new-onset seizure activity. Apart from the routine investigations, culture and antibody assays should be sent for opportunistic infections due to VZV, CMV, HHV 6 and JE virus. A cytological examination for abnormal cells is also warranted in such patients [6]. PCR has good specificity for CMV (95%) and *Toxoplasma* (100%) but lower sensitivity (79% and 42%, respectively) [2].

It is important to remember that there are no absolute or even range values and clinical correlation remains imperative. Reasons for a lack of classical CSF findings in bacterial meningitis are given in Table 3.5. In bacterial meningitis, CSF Gram stain will indicate organisms in 60–90% of cases and positive cultures in 80% of cases [18]. Ninety percent of patients will have a CSF cell count of >100 WBC/mm³, and ~60% of patients will have cell counts of >1000 WBC/mm³ [19]. CSF glucose levels are <40 mg/dL in 50–60% of patients, and using a CSF/serum glucose ratio of ≥0.4 is 80% sensitive and 98% specific in children >2 months of age [20]. CSF glucose also may be reduced in fungal, tuberculous or carcinomatous meningitis. The CSF protein level is the most resistant to rapid change, remaining elevated for 10 days or more [21].

CSF sterilization may occur more rapidly after initiation of parenteral antibiotics than previously suggested, with complete sterilization of meningococci within 2 h and the beginning of sterilization of pneumococci by 4 h of therapy. Lack of adequate culture material may result in an inability to tailor therapy according to antimicrobial susceptibility or in unnecessarily prolonged treatment if the clinical presentation and laboratory data cannot exclude the possibility of bacterial meningitis [22].

CSF pleocytosis is a characteristic of HIV disease, which varies significantly with easily identifiable clinical and laboratory features. Use of antiretroviral agents decreases the chances of pleocytosis. This association may be stronger when the regimen contains two or more agents with good CNS penetration [23].

Table 3.5 Reasons for a lack of classical CSF findings in bacterial meningitis

- Partially treated meningitis (e.g. prior antibiotics)
- Time of lumbar puncture (is it early in course of the disease before the patient mounts a response or late in the course?)
- The patient's condition (is the patient able to mount a response to the invading organism or is the patient immunosuppressed or has an overwhelming infection?) [17]

Seizures alone generally do not cause abnormalities in the CSF, so abnormal findings on CSF should not automatically be attributed to a seizure [24]. Neonatal meningitis frequently occurs in the absence of bacteraemia and in the presence of normal CSF parameters. No single CSF value can reliably exclude the presence of meningitis in neonates. The CSF culture is critical in establishing the diagnosis of neonatal meningitis [25].

Other CSF Tests in Neuroinfections

Antibodies

In patients with HSV encephalitis, the intrathecal synthesis of HSV-specific antibodies can be detected within 8–12 days and sometimes longer after the onset of symptoms. These antibodies remain positive for as long as long as 30 days; in some series they have been detected as long as 3 months after the onset of neurological symptoms [26]. Anti-HSV1 antibody has a sensitivity of 50% at day 10 if a retrospective diagnosis is considered useful. The HSV antibody assay is performed on serum and CSF; a < 20:1 serum/CSF ratio of antibodies to HSV1 suggests intrathecal synthesis of antibodies [26]. In a study of 787 samples of episodes likely to be CNS viral infections, 30% were PCR-positive compared with 5% categorized as unlikely [27]. The most frequent positive findings were EBV, enteroviruses and HSV. Enteroviruses and HSV were found predominantly in the likely CNS viral infection group, whereas EBV was found mainly in the unlikely group. Positive PCR results were more likely when there were 3–14 days between symptom onset and LP and when CSF WBC count was abnormal. A normal CSF WBC count, however, did not exclude a viral infection [27]. The sensitivity of CSF IgM in JE was 80–90% compared with 10% in serum [28].

Lactic Acid

CSF lactic acid has been used when a patient has had prior antibiotic therapy, which probably makes the CSF culture- and Gram stain-negative. It has also been used to distinguish between bacterial and aseptic meningitides [29]. In bacterial or fungal meningitis, the CSF lactic acid is elevated, whereas it is generally normal (normal CSF lactic acid <35 mg/dL) in viral infections [30]. In postoperative neurosurgical patients, however, a CSF lactate concentration cut-off of 4 mmol/L was found to be superior to the CSF/serum glucose ratio for the diagnosis of bacterial meningitis. The sensitivity was 88% and specificity was 98%. The positive predictive value was 96%; negative predictive value was 94% [31].

Adenosine Deaminase (ADA)

CSF ADA has the disadvantage of low specificity and is raised in lymphomas, malaria, brucellosis and pyogenic meningitides [8]. A recent study in HIV-infected adults reported a diagnostic sensitivity of 57% with false-positive tests observed in cerebral CMV infection, cryptococcal meningitis and cerebral lymphomas [32].

Protein 14-3-3

14-3-3 immunoassay on CSF has been shown to be useful for the diagnosis of Creutzfeldt-Jakob disease (CJD) in select patients with dementia and myoclonus or ataxia. Diseases that cause false-positive results are numerous and include HSV encephalitis, bacterial and tuberculous meningoencephalitis, recent cerebral infarction, degenerative dementias (including Alzheimer disease), carcinomatous meningitis, paraneoplastic neurological disorders, anoxic encephalopathy, MS, mitochondrial encephalomyopathy, cerebral amyloid angiopathy and Hashimoto encephalopathy, among others [14]. The highest sensitivity for 14-3-3 and Tau was seen in sporadic CJD (85% and 86%), and a combined determination of 14-3-3 and Tau, S100b, or neuron-specific enolase (NSE) increased the sensitivity to >93% [33].

CSF Diagnostic Tests for Non-infective Aetiologies

Non-infective aetiologies presenting as neurological emergencies with either CSF lymphocytic pleocytosis or albumino-cytological dissociation are few but should not be missed and require a high index of suspicion. These include the following:

1. Leptomeningeal metastases
2. Chemical meningitis after chemotherapy
3. Subarachnoid haemorrhage
4. ADEM
5. Behçet disease
6. Neurosarcoidosis
7. Guillain-Barré syndrome (GBS) (CSF is not an emergency procedure in this case)

A definitive diagnosis of leptomeningeal metastases (LM) requires the identification of malignant cells in the CSF. Two or three samplings of CSF may be required before malignant cells are detected. The diagnostic yield of CSF samples obtained in the emergency department can be optimized through the collection of at least 10 ml of CSF for cytological examination and the prompt delivery of the specimen to the laboratory. Characteristic CSF abnormalities in LM include an elevated opening pressure in >50% of patients, mononuclear pleocytosis in >70% of patients, elevated protein in ~80% of patients and decreased glucose in 25–30% of patients. The range of CSF protein elevation in LM is wide, with a median total protein concentration of 1 g/L [34].

Acute encephalopathy characterized by seizures, altered mental status and lethargy may occur within 24–48 h of intrathecal (IT) methotrexate or cytosine arabinoside. The treatment is symptomatic, and symptoms generally resolve completely. In addition, concurrent IT chemotherapy and spinal irradiation may cause a transverse myelopathy. Back or leg pain, paraplegia, sensory loss and bowel/bladder dysfunction typically develop within 48 h of IT chemotherapy but may occur anytime from up to within 30 min to 2 weeks following treatment. The CSF is found to have elevated protein levels, and MRI shows expansion of the spinal cord and hyperintensity

on T₂-weighted sequences. The prognosis for recovery is poor with persistent paresis in ~60% of those affected [35].

Subarachnoid haemorrhage is not an indication for LP, but in cases of normal CT scan with thunderclap headache, the sensitivity, specificity, positive predictive value and negative predictive value of CSF xanthochromia for the detection of cerebral aneurysms were 93%, 95%, 72% and 99%, respectively [36].

In GBS there is albumino-cytological dissociation about 1 week after the onset of symptoms and the CSF has been reported to have predictors of prognosis to identify patients who are likely to make a poor recovery and to guide therapeutic decision-making in the acute phase [37]. In a prospective multicentre study including 132 patients (38 GBS, 38 neurological controls, 42 headaches, 14 chronic inflammatory demyelinating neuropathy), CSF levels of axonal (neurofilament [NfH] and Tau) and glial (S100B and glial fibrillary acidic protein) protein biomarkers were measured on admission and high NfH levels (>0.73 ng/mL) predicted poor outcome, as did high Tau levels [37].

Conclusion

CSF examination has a vital role in neurological emergencies. Apart from stat laboratory information which helps in making quick decisions, newer antigen, antibody, tumour markers and proteins are developing increasing diagnostic and prognostic usefulness. Whereas PCR assays are the gold standard for detecting specific viruses, agglutination tests and surrogate markers, such as lactate and ADA levels, are supplementary in cases in which a definitive diagnosis is difficult and the CSF cultures are negative.

EEG in Neurological Emergencies

Overview

The utility of any diagnostic tool in the emergency room depends on the ease of its use and the precision of the obtained results. The electroencephalogram (EEG) is a relatively innocuous, noninvasive, readily available investigation and can quickly generate clinically useful data provided it is intelligently used, its limitations understood and its findings interpreted in the clinical context. Although there are hardly any clinical entities among the neurological emergencies where an EEG may be considered pathognomonic, yet findings on the EEG can help make clinical decisions and guide management in many seriously ill patients. Making the EEG work for you is probably most dependent on learning and understanding not just the strengths of the EEG but also keeping in mind its limitations. Just ordering an EEG for every patient who is very sick, without having a clear idea about what you want to see or rule out, will make the EEG a futile exercise and only be a waste of precious time and resources. Findings on the EEG may suggest a diagnosis, but

sometimes, not seeing a particular abnormality is also an important observation. Another caveat that is frequently overlooked and an important cause of misinterpretation of the EEG is the dynamic nature of EEG findings (Figs. 3.1, 3.2 and 3.3). What one sees or does not see at any particular time in a given patient may drastically change if the EEG is repeated after some drug has been administered or even over time without any medical intervention. So, if one strongly expects some specific findings on EEG and they are not present on the first examination, repeating the EEG after some time has elapsed may not be a bad idea.

An EEG may be used to answer clinical questions in several contexts, but if we limit our consideration to seriously ill patients, then the EEG may be employed either as an emergent EEG (eEEG) or a continuous EEG (cEEG). A cEEG is an ongoing EEG monitoring strategy for the assessment of brain function in critically ill patients. As cEEG is a tool for inpatient evaluation and monitoring and not an investigation of choice or utility in a sick patient presenting to the neurology emergency, it will not be discussed any further in this chapter.

Emergent EEG or eEEG is that EEG which is ordered on a non-elective basis and performed expeditiously. The exact timeframe within which it is acceptable to perform an eEEG after it is requisitioned remains variable and is as much guided by the



Fig. 3.1 Generalized periodic discharges (GPDs) in the EEG of a patient with NCSE. The patient had presented in a state of irrelevant talking, inappropriate behaviour and looking confused for >24 h



Fig. 3.2 A 12-year-old male patient presented to the emergency with injury to the forehead due to a fall. History of recent scholastic decline with 'jitteriness' was given by his mother. A final diagnosis of subacute sclerosing panencephalitis was made in this patient. EEG (at a paper speed of 10 mm/s) shows long interval diffuse discharges recurring at a frequency of about 1/8–10 s. The accompanying video showed the patient having generalized myoclonic jerks with slow relaxation almost time-locked with the EEG complexes

perceived seriousness and need in a given patient as it is dictated by the availability of dedicated equipment and EEG technicians. A generally acceptable gap between the request for EEG and start of the record is 1 h. Whether an eEEG is performed for an indoor patient to resolve a diagnosis or detect the cause for deterioration, or for a patient presenting to the neurology emergency for the first time, the urgency remains unchanged. There are, however, some differences between these two eEEGs carried out in the indoor and emergency settings. When eEEGs are performed for indoor patients, several important facts about patients' clinical history, course of illness and results from other relevant investigations are already available. The availability of all these data means that the eEEG performed for an indoor patient is to seek answers to specific questions and to attempt to rule in, or rule out, limited clinical diagnoses. In the neurology emergency, this advantage of having specific clinical entities in mind is generally not present. When eEEG is performed in the emergency, results from other ancillary investigations are usually only partially available or not available at all. The clinical history and course of illness, too, may



Fig. 3.3 A 55-year-old lady presented with a few months' history of progressive cognitive decline and mild ataxia. Her husband had noted myoclonic jerks recently. A diagnosis of Creutzfeldt-Jakob disease was considered in view of the clinical presentation and MRI findings. Her EEG showed the typical 1–1.5 Hz periodic complexes with occasional triphasic morphology

or may not have been fully clarified by the time an eEEG is performed. This makes interpretation of the eEEG performed in the neurology emergency that much more complex and challenging. Therefore, an eEEG in the neurology emergency needs to be interpreted with far more skill and caution than an EEG performed in most other situations.

The most important question an eEEG attempts to answer is: Is a patient's altered sensorium due to an epileptic event or not?

When Should an eEEG Be Ordered in the Neurology Emergency?

Many neurological emergencies are accompanied by an alteration of sensorium to a greater or lesser extent. However, the assumption that an EEG will help in the management of each of these patients and therefore should always be ordered is not correct. As organizing the EEG in an emergency and ensuring that a technically acceptable record is procured can be difficult, therefore, it needs to be requested and used thoughtfully. Precise, evidence-based guidelines are not available to help decision-making regarding the utility of an EEG in each specific situation. However, there is a broad consensus that an EEG should be done for every

patient presenting with an altered mental status, confusion or decreased level of consciousness where a non-convulsive status epilepticus (NCSE) is suspected or other available clinical and paraclinical data do not explain the patient's sensorial abnormality [38–40].

Specifically, recommendations [41, 42] have proposed that an eEEG be obtained for:

1. *Persistent altered consciousness:*

- (a) Without a reasonable explanation from known iatrogenic (e.g. recent anti-convulsant drug loads), clinical, radiological and metabolic parameters.
- (b) With signs suggestive of seizures such as blinking, ocular jerks, limb twitches, tongue and lip movements, tachycardia and altered respiratory patterns. If there are clear clinical signs of seizure activity, with a correlation confirmed by a prior EEG, then these clinical signs can be followed for an evaluation of therapeutic efficacy, and EEG monitoring is not entirely necessary.
- (c) If there was an observed seizure but the patient is not regaining full consciousness quickly enough.
- (d) Diagnosis of Hashimoto coma.

2. *Refractory status epilepticus:* This is the universally accepted indication for eEEG where it helps to evaluate the possibility of either continuing 'subtle status epilepticus' or NCSE [43]. Non-convulsive status may be diagnosed in up to 20% of patients in the ICU who have unexplained alterations in consciousness during a cEEG monitoring [44]. These data, however, pertain to critically ill inpatients in the ICU and not to the patients presenting for the first time in an emergency with an unexplained altered sensorium where such data are not available. An NCSE may be suspected and an eEEG done in the following circumstances:

- (a) After the treatment of overt seizures or status epilepticus, when the patient fails to wake up within the expected amount of time.
- (b) There is no clear underlying process (anoxic/metabolic/stroke/subarachnoid haemorrhage), but the patient is still confused or drowsy.
- (c) One important indication is also to diagnose refractory seizure-like motor activity in a patient with psychogenic non-epileptic seizures (PNES) [45]. A video EEG would be the desired investigation in these circumstances so that the electro-clinical correlation can be determined. However, if no video is available, a nurse or family member can help by annotating the EEG when an event occurs. Video may additionally help to eliminate the confounding movement artefacts induced in the EEG and allow a detailed study of the clinical event.

3. *Pharmacologically managed sedation and coma:* This would mostly necessitate a cEEG and is beyond the scope of the chapter.

4. *For the diagnosis of viral encephalitis:* In any suspected case of acute encephalitis since it may help in distinguishing focal encephalitis from generalized encephalopathy. Some EEG changes may be relatively specific, for example,

periodic lateralized epileptiform discharges (PLEDs) in herpes simplex encephalitis (HSE) [46].

5. *Brain death:* In general, an EEG is neither necessary nor sufficient for determination of brain death [47].

- (a) The wording of the EEG interpretation is ‘electrocerebral inactivity’ (silence) which may have several aetiologies. Brain death is a clinical diagnosis.
- (b) A flat EEG in the presence of hypothermia (temperature < 92 °F) is consistent with brain death.
- (c) A flat EEG in the presence of CNS-depressant medications (usually anticonvulsants), as long as blood levels are not above the middle therapeutic range, is consistent with brain death.

About 6–12% of EEGs are ordered ‘stat’ [48, 49]. The implications of stat or emergent in the true sense means that the staff or physician involved should interrupt the present schedule to perform the procedure immediately and the procedure should be done regardless of the time of the day.

Practical Considerations when Ordering an eEEG

It should be kept in mind that an eEEG requires time for conducting as well as personnel for both performing the test and for interpretation. With increasing use of the EEG in critically ill patients, the terminology that is used to describe the various components of the EEG and also their implications has expanded. Familiarity with this standard terminology is essential for any clinician or electroencephalographer but is beyond the scope of this chapter [50, 51]. The practical considerations are as follows:

1. If the patient is recovering from a seizure, but too slowly, will the delay affect the outcome?
2. Are there clinical signs of ongoing seizure activity which can be followed easily instead of repeating an EEG?
3. As it might take the technologist 2–3 h to start the EEG, it is advisable in the meantime to schedule other tests, e.g. CT scan and MRI, so that the technologist does not waste any time.
4. Will the results of an eEEG change your immediate plans? For example, if a patient is already under sedation.
5. It is advisable to consult the Epilepsy/EEG Fellow. This would also help in expediting the interpretation.

What Questions Does an eEEG Answer?

The utility of an eEEG lies in timely diagnosis and management. The findings in the eEEG help in determining whether the clinical condition is epileptic or

non-epileptic. An attempt should be made to answer the following questions when interpreting an eEEG:

1. Is it artefactual or real brain activity? Like any other EEG interpretation, this is an important consideration, especially whether the event is epileptiform or myogenic.
2. Is it an electrographic seizure activity? This is especially important in deciding on the diagnosis of NCSE.
 - (a) *Repetitiveness*. The more evenly spaced the discharges, the more likely it is to be a seizure. Repetitive slow waves may be a seizure discharge.
 - (b) *Rhythmicity*. The more rhythmic the discharges, the more likely it is to be a seizure. Rhythmic slow waves may be a seizure discharge.
 - (c) *Organization*. A seizure has structure, with a beginning, often leading into a gradual increase in amplitude and frequency, followed by a period of gradual decrease in amplitude and frequency. The event should last for at least 10 s to be considered an electrographic seizure.

What Questions Can an eEEG Not Answer?

These would fall under two categories.

1. Situations for which an eEEG should not be requested:
 - (a) Certification of brain death
 - (b) When there is a clear cause for change in mental status
2. Patterns which are controversial and of uncertain significance:
 - (a) PLEDs. Although the majority of patients with PLEDs will have a clinical seizure during their hospital course so that they should be on routine levels of an anticonvulsant drug, some regard PLEDs as a form of status and treat them as such.
 - (b) *Post-anoxic EEGs*. These may have PLEDs, BiPLEDs or a burst-suppression EEG. The presence of any of these more than 12 h after the incident (at a time when the patient is not on any CNS-suppressant medication) indicates a very poor prognosis. These might thus be more of an aid in prognostication rather than in emergent management.

Conclusion

To conclude, only broad guidelines rather than clear recommendations may be made for ordering an eEEG on the basis of available data. Each centre needs to consider the access to technical personnel and equipment, other technical aspects and local practice patterns and limit performance of eEEGs in the emergency to a level where it remains both a meaningful and a well-utilized investigation in the emergency department. The widely prevalent practice of neurological consultation

before obtaining an eEEG seems prudent, given that EEG interpretation is a further specialization within the field of neurology. There should be a high index of suspicion of NCSE in an appropriate clinical setting, and an eEEG should be considered in all patients suspected of being in a NCSE.

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Coma and Encephalopathy

4

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Introduction

The term *encephalopathy* refers to a syndrome of global brain dysfunction that can be caused by a variety of different causes, each with a different prognosis and implication for diagnosis and management. The hallmark of encephalopathy is an altered mental state. The common neurological symptoms of encephalopathy are loss of cognitive function, subtle changes in personality, inability to concentrate, lethargy and depressed consciousness. The other neurological signs that may be present include myoclonus, asterixis, nystagmus, tremors, seizures and respiratory abnormalities, such as Cheyne–Stokes respiration, apneustic respiration and post-hypercapnic apnoea.

The Basis of Consciousness

Consciousness depends upon the alerting or awakening role of an intact ascending reticular activating substance (RAS) in the brain stem, together with a functioning cerebral cortex of both hemispheres which determines the content of that consciousness. The ascending RAS is a ‘continuous isodendritic core, extending from the medulla through the pons to the midbrain, and is continuous caudally with the reticular intermediate grey lamina of the spinal cord and rostrally with the subthalamus, hypothalamus and thalamus. Its functions and interconnections are considerable and its role greater than that of a simple cortical arousal system’ [1, 2]. The neurotransmitters involved in this arousal system are not fully determined, though it is likely that cholinergic and monoaminergic neurotransmitters as well as gamma aminobutyric acid (GABA) may have a role in controlling consciousness [3–5].

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Unlike discrete cortical functions such as language or vision, which are focally located within the cortex, the content of consciousness can best be regarded as the amalgam of all cognitive functions. Coma arising from disruption of this cortical activity is due to a diffuse pathology, such as global hypoxia or ischaemia seen usually after cardiac arrest or anaesthetic accidents, or the effects or presumed cortical vasospasm seen in infective meningitis, or the chemical meningitis following subarachnoid haemorrhage (SAH), in which diffuse cortical ischaemia is supposed to cause disruption of function [1, 2].

‘There is a continuum from the individual in full consciousness to the patient in an unarousable coma.’ The terminology that is usually employed derives from the Brain Injuries Committee of the Medical Research Council (MRC), UK [6].

- *Confusion:* This is defined as disturbance of consciousness characterized by impaired capacity to think clearly and perceive, and to respond to and remember current stimuli, and the presence of disorientation. Confusion involves a generalized disturbance of cortical function which is usually associated with electroencephalographic (EEG) abnormalities.
- *Delirium:* This is defined as a state of disturbed consciousness with motor restlessness, transient hallucinations, disorientation and perhaps delusions.
- *Obtundation:* Defined as a disorder of alertness, associated with psychomotor retardation.
- *Stupor:* This is defined as a state in which the patient, though not unconscious, exhibits little or no spontaneous activity. Although the individual appears to be asleep, he or she may be awakened to vigorous stimulation but show limited motor activities and usually fail to speak.
- *Coma:* This is defined as a state of unarousable psychological unresponsiveness, in which subjects lie with their eyes closed and show no psychologically understandable response to external stimuli or inner need. This implies both a defect in arousal and in awareness of self and environment.
- *Vegetative state:* When the cerebral cortex recovers more slowly than the brain stem or when the cortex is irreversibly damaged, there may arise a situation in which the patient enters a vegetative state without cognitive function. It may be a transient phase through which patients in coma pass as they recover or deteriorate. For example, after a severe anoxic injury to the brain, a state develops in which the brain stem recovers function, but the cerebral hemispheres are not capable of recovery. This is the state of ‘persistent vegetative’ condition described by Jennett and Plum [7]. Such patients may survive for long periods, on occasion for decades, but never recover outward manifestations of higher mental activity.
- *Akinetic mutism:* This is a similar condition of unresponsiveness but apparent alertness, as demonstrated by reactive α - and β -EEG rhythms in response to stimuli. The major difference between akinetic mutism and the vegetative state is that in the former, patients have a flaccid tone and are unresponsive to peripheral pain. It is thought that this state is due to bilateral frontal lobe lesions, diffuse cortical lesions or lesions of the deep grey matter.

- *The locked-in syndrome:* This is a deafferented state caused by bilateral ventral pontine lesions involving damage to the corticospinal, corticopontine and corticobulbar tracts. The patient has total paralysis below the level of the third nerve nuclei and, although able to open, elevate and depress the eyes, has no horizontal eye movements and no other voluntary eye movement. Similar states are occasionally seen in patients with severe polyneuropathy or myasthenia gravis and after the use of neuromuscular blocking agents.

Aetiology

The aetiology of coma may be classified into two broad categories: structural or surgical (Table 4.1) and medical or metabolic (Table 4.2).

Approach to Diagnosis

The onset of coma will also give a lead to the diagnosis. A sudden onset of non-traumatic coma indicates a vascular cause, as against a condition with a more protracted course, such as tumour, abscess or infections. A detailed physical examination may provide clues to the aetiology of the patient's symptoms [8–12].

Table 4.1 Aetiology of structural/surgical coma

• Trauma
Subdural injury
Epidural injury
Diffuse axonal injury
Brain contusions
Penetrating head injury
• Intracranial haemorrhage
Subarachnoid haemorrhage
Intracerebral haemorrhage: Pontine, cerebellar, basal ganglia, lobar
• Ischaemic stroke
Large middle cerebral artery infarction with brain herniation
Brain stem stroke involving bilateral rostral pons or midbrain
'Top of basilar' syndrome with bilateral infarction of thalamci and rostral midbrain
• Diffuse microvascular abnormality
Thrombotic thrombocytopenic purpura
Haemorrhagic viral/rickettsial fevers
Cerebral malaria
• Tumour
Primary brain tumour with herniation
Multiple metastatic lesions, etc.
• Other disorders
Central pontine lesions

Table 4.2 Aetiology of metabolic/medical coma

<ul style="list-style-type: none"> • Drugs Benzodiazepines, barbiturates, opioids, tricyclic agents, etc. • Infectious diseases Septicaemia Meningitis, especially bacterial Encephalitis (e.g. herpes simplex, arboviral infection) • Endocrine disorders Hypoglycaemic coma Diabetic ketoacidosis Hyperosmolar coma Myxoedema Hyperthyroidism • Metabolic abnormalities Hyponatraemia Hypernatraemia Uraemia Hepatic encephalopathy Hypertensive encephalopathy Hypomagnesaemic pseudocoma 	<ul style="list-style-type: none"> • Toxic reactions Carbon monoxide poisoning Alcohol intoxication Acetaminophen overdose Ethylene glycol poisoning Other poisoning • Medication side-effects Reye syndrome Neuroleptic malignant syndrome Central anticholinergic syndrome Serotonin syndrome Isoniazid intoxication • Deficiency states Thiamine deficiency (Wernicke encephalopathy) Niacin deficiency (pellagra) • Hypothermia • Psychogenic coma
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General Physical Examination

Blood Pressure

Look for hypotension or hypertension. Long-standing hypertension predisposes an individual to intracerebral haemorrhage (ICH), ischaemic stroke and hypertensive encephalopathy. This may, however, also be a consequence of the process causing the coma (ICH, SAH).

Temperature

Hypothermia: This can occur in ethanol or sedative drug intoxication, Wernicke encephalopathy, hepatic encephalopathy and myxoedema.

Hyperthermia: This can occur in status epilepticus, pontine haemorrhage, heat stroke, malignant hyperthermia and anticholinergic intoxication.

Posture

Look for muscle jerks or tremors. Inspect the respiratory movements for tachypnoea, bradypnoea, Cheyne–Stokes breathing or Kussmaul breathing.

Colour

Look for pallor, icterus, cyanosis of methaemoglobinæmia and the cherry-red colour of carbon monoxide haemoglobin.

Facial Muscles

Look for asymmetry of the face. This may indicate hemiplegia. Abnormal twitching or grimacing may suggest seizures.

Oral Cavity

Look for lacerations of the tongue. These may indicate a bite during a convulsive seizure. Smell the breath for alcohol or ammonia.

Ears

Look for pus, perforation or discharge.

Neck

Test for nuchal rigidity, Brudzinski sign and Kernig sign. These are evidence of meningeal irritation.

Optic Fundi

Look for papilloedema or retinal haemorrhage, which may indicate chronic or acute hypertension or an elevation in intracranial pressure. Subhyaloid haemorrhages in an adult suggest SAH.

Signs of Trauma

Look for the Battle sign (swelling and discolouration over the mastoid bone behind the ear), raccoon eyes (periorbital ecchymosis), cerebrospinal fluid rhinorrhoea or otorrhoea and skull fractures.

Neurological Evaluation

The examination needs to be done promptly, keeping in view the time-sensitive nature of the therapy required. The examination has four important components:

- Respiratory patterns
- Pupillary responses
- Eye movements
- Motor responses

Respiratory Patterns

Breathing patterns can provide useful information regarding the cause of the coma but are often ignored and missed because of the widespread use of mechanical ventilation.

Cheyne–Stokes respiration is a respiratory pattern that oscillates between hypoventilation and hyperventilation. It usually results from bilateral cortical or diencephalic insult but may occur as a result of damage anywhere between the forebrain and pons. Stable Cheyne–Stokes breathing usually portends a good prognosis. However, in a patient with a unilateral mass lesion, the onset of Cheyne–Stokes breathing may signify impending herniation.

Short-cycle periodic breathing is similar to Cheyne–Stokes but has a faster cycle, with one or two waxing breaths, followed by three or four rapid breaths and then one or two waning breaths. It is the result of increased intracranial pressure, expanding posterior fossa lesions, or a lower pontine lesion.

Central neurogenic hyperventilation usually results from lesions of the centrum tegmentum of the pons, ventral to the aqueduct or the fourth ventricle. Patients breathe 40–70 times per minute. It is important to distinguish central neurogenic hyperventilation from pulmonary disorders. In general, CNS lesions cannot be blamed for hyperpnoea if the PO₂ is <80 mmHg or PCO₂ is >40 mmHg.

Apneustic breathing consists of a prolonged inspiratory gasp with a pause at the end of inspiration, followed by expiration. Apneustic breathing is caused by lesions of the dorsolateral lower half of the pons.

Cluster breathing results from high medullary damage and involves periodic breathing with irregular frequency and amplitude, along with variable pauses between clusters and breaths.

Ataxic breathing is irregular both in rate and rhythm. It is caused by medullary lesions and is usually a preterminal pattern.

Pupillary Responses

Examination of the pupils is of paramount importance in a patient with coma. Pupils that are equal in size and reactive to light make brain herniation or a neurosurgical emergency less likely. An unreactive, unequal and dilated pupil may be a sign of herniation of the uncus and represents a neurosurgical emergency. Pressure on the third nerve after it exits from the midbrain results in failure of parasympathetic innervation to the eye. Pontine lesions disrupt sympathetic pathways and cause ‘pinpoint’ pupils, which are reactive to light but may be seen only through a magnifying glass. A comatose patient presenting with pinpoint pupils should be suspected of having a pontine haemorrhage or large brain stem or pontine infarction.

The common differential diagnoses are:

- Bilateral dilated pupils:
 - Transtentorial herniation of both medial temporal lobes
 - Anticholinergic or sympathomimetic drug intoxication
- Bilateral pinpoint pupils:
 - Morphine poisoning
 - Pontine haemorrhage
 - Neurosyphilis
 - Organophosphate poisoning
 - Miotic eye drops
- Asymmetric pupils (anisocoria):
 - A difference of <1 mm may be normal in 20% of the population.
 - Impending herniation.
- Fixed mid-sized pupils:
 - Midbrain lesion

Eye Movements

There are three steps in the evaluation of eye movements:

- Observing the resting position of the eyes
- Evaluating spontaneous eye movements
- Testing reflex eye movements

The resting position of the eyes in an unresponsive patient may be disconjugate in the horizontal plane. Vertical displacement of the eyes is known as ‘skew’ deviation and usually indicates a brain stem lesion.

Roving, slow, conjugate horizontal, to-and-fro movements are usually seen in metabolic encephalopathies or bilateral lesions above the brain stem. *Ocular bobbing* consists of a rapid downward jerk of both eyes, followed by slow return to mid-position. *Ocular dipping* is a movement reverse to the above, i.e. a slow downward phase followed by a rapid upward phase and preserved reflex eye movements. When the spontaneous movements occur from mid-position upwards, the terms used are ‘reverse’ ocular bobbing and ‘reverse’ ocular dipping. The presence of these movements indicates a brain stem lesion or, occasionally, a cerebellar lesion or diffuse cerebral damage.

Paralysis of reflex and spontaneous lateral eye movements tend to be associated with acute pontine lesions. Examination of the reflex eye movements consists of the ‘oculocephalic’ reflex and the ‘oculovestibular’ reflex. Oculocephalic reflex is commonly referred to as ‘doll’s eyes’. When the head is rotated laterally in a patient with intact brain stem function, the eyes should move in a direction opposite to the movement of the head. The absence of this response may indicate brain stem dysfunction. The oculocephalic reflex should never be checked until the stability of the neck is ensured. For oculovestibular or caloric testing, the integrity of the tympanic membrane is first ascertained, and then 40–60 ml of ice cold water is used to irrigate the ear. If the brain stem is intact, the eyes deviate to the side of the cold water. The fast corrective component of eye movement is away from the stimulated ear. The latter movement is dependent upon cortical function and is absent in a comatose patient; only the slow phase towards the stimulated ear should be present. The absence of response to caloric testing may suggest brain stem dysfunction.

Motor Responses

The presence of spontaneous, purposeful motor movements in a patient with coma is a good prognostic sign. If the patient spontaneously moves only one side, a hemispheric or brain stem lesion is probably present contralateral to the side not moving. If there are no spontaneous movements, a stimulus with increasing severity and finally a noxious stimulus, such as nail bed or supra-orbital pressure, should be applied.

Decorticate posturing (flexion at the elbow and wrist bilaterally, with shoulder adduction and extension of the legs) suggests a lesion above the brain stem, specifically the red nucleus. *Decerebrate posturing* (internal rotation and adduction of the shoulder with extension at the elbows, wrists and legs) is usually associated with a bilateral midbrain or pontine lesion. This lesion is classically at the level of the red nucleus in the midbrain. Occasionally, metabolic encephalopathies, such as hypoglycaemia, may produce a similar picture. In general, decerebrate posturing has a worse prognosis than that of decorticate posturing. *Myoclonus* consists of nonrhythmic jerking movements in single or in multiple muscle groups and is usually associated with anoxic injuries (cortical reflex myoclonus) or metabolic encephalopathies, such as hepatic encephalopathy. Rhythmic myoclonus suggests a brain stem injury. The clinical features which help in the localization of brain lesions in a patient with encephalopathy are given in Table 4.3 [9].

Table 4.3 Localization of brain lesions in a comatose patient

Site	Mental status	Pupillary size	Eye movements	Motor features	Respiration
Diencephalon	Drowsy	Small	Normal	Abnormal flexion	Cheyne–stokes
Midbrain	Coma	Fixed in mid-position	Dysconjugate	Abnormal extension	Hyperventilation
Pons	Coma	1 mm	Complete paralysis	Abnormal extension	Hyperventilation
Medulla	Variable	Variable	Variable	Flaccid	Apnoea, circulatory collapse

Box 4.1: Differential Diagnoses of CT-negative, Non-febrile Comas

1. Hypoxic–ischaemic encephalopathy
2. Non-convulsive status epilepticus
3. Static encephalopathy
4. Hepatic encephalopathy
5. Uraemic encephalopathy
6. Wernicke encephalopathy
7. Hypertensive encephalopathy
8. Toxic encephalopathy
9. Metabolic encephalopathy
10. Lyme encephalopathy
11. Mitochondrial encephalopathy
12. Glycine encephalopathy
13. Hashimoto encephalopathy
14. Transmissible spongiform encephalopathy

Issues in Differential Diagnosis and Management

The initial care of a patient in coma must be resuscitation by ensuring adequate oxygenation and circulation. A sample of blood should be withdrawn to estimate glucose and other parameters. Once stability is ensured, it is imperative to obtain an adequate history from those who have brought the patient to the accident and emergency department or those who were responsible for previous care. An assessment of the level of coma follows, with an evaluation of other features that may give clues to the aetiology, as discussed previously. The relevant investigations may then be considered, including biochemical and serological assessments, imaging and the possibility of EEG. The important differential diagnoses of CT-negative, non-febrile coma are outlined in Box 4.1. Lumbar puncture will be indicated in certain circumstances. With these investigations, the diagnosis of the aetiology of coma may be established and corrective therapies instituted. Patients presenting to hospital in coma or lapsing into coma are ideally treated in an intensive care unit or a high

dependency unit. The cause of coma and the prognosis of the patient will determine further management.

Among the many differential diagnoses of comatose patients, the following commonly encountered encephalopathies, not described in detail elsewhere in this book, and a few interesting, relatively newly recognized entities will be discussed.

Hypoxic–Ischaemic Encephalopathy [13–16]

This results from decreased brain perfusion, oxygenation or both. Decreased perfusion alone may be due to cardiac arrhythmia or arrest or due to severe heart failure. The brain is differentially susceptible to hypoxia, hypoglycaemia and hypoperfusion. In general, the areas most susceptible to hypoxia have the greatest required metabolic rate for glucose utilization and ATP requirement. In the case of cardiac arrest or ventilatory failure, they suffer first and most severely. Clinical patterns of circulatory arrest can be varied and are outlined in Box 4.2. In general, respiratory

Box 4.2: Clinical Patterns of Circulatory Arrest

Brain stem coma

1. *Prolonged hypoperfusion—anoxia*
 - Dilated pupils
 - Absent corneal reflexes
 - Absent doll's eye movements
 - Cold caloric test negative
 - Frequent loss of spontaneous respiration
 - No spontaneous movements/decorticate/decerebrate posturing
2. *Selective necrosis of brain stem nuclei*
 - Usually affects infants and children
 - No oculocephalic eye movements
 - Stiff extremities
 - Autonomic movements with stimuli
 - Autonomic disinhibition
 - Loss of spontaneous respiration
3. *Brain stem coma secondary to bi-hemispherical coma*

Coma due to bilateral hemispheric dysfunction

- Unresponsive to noise, bright light or voice
- Responds to painful stimuli
- Spontaneous movements of the extremities
- Pupils are normal or small; react to light
- Eye movements may be roving, midline, deviated upwards or exhibit hyperactive doll's eyes
- Gag reflex intact, spontaneous blink and swallow reflexes

arrest without circulatory compromise carries a better prognosis. Progression from bi-hemispheric coma may show specific features of selective vulnerability to the anoxic–ischaemic episode. Many patients demonstrate agitation, restlessness, confusion and delirium as they regain consciousness. Less severe insults may produce a predominant corticospinal tract dysfunction or syndrome, with intact corticospinal tract signs. A syndrome of delayed leukoencephalopathy is generally seen in young patients who have suffered strangulation, drowning, inhalation of noxious gases or carbon monoxide poisoning. Pathologically, there is diffuse demyelination to haemorrhagic white matter necrosis, with basal ganglia involvement. The clinical features include initial coma associated with quadriplegia, involuntary limb movements and atonia. This condition progresses to a dystonic rigid state, with relative preservation of the cortex, and severe damage of the basal ganglia and generalized demyelination. Delayed deterioration starts between 4 and 10 days in some patients. Many studies on prognostic indicators in patients who have suffered hypoxic–ischaemic injury have been published in the literature, but no single factor can be specific in prognosticating with certainty [17–23]. A few features are outlined in Box 4.3. A systematic review of the studies carried out was published as a scientific statement by the American Academy of Neurology, and the reader is referred to the same for a detailed review [24].

Box 4.3: Some Prognostic Signs After Hypoxic–Ischaemic Encephalopathy
Evoked and spontaneous limb movements

1. Spontaneous limb movement—good prognostic sign.
2. Evoked decerebration and decortications—poor prognostic sign.
3. Myoclonus: persistent and stimulus sensitive—poor prognostic sign.
4. Seizure—first 24 h are not prognostic but status epilepticus is a poor sign.

Late prognostic signs (24 h) [21]

Good

- Awake and alert
- Return of brain stem reflexes
- Eye opening with ocular fixation reflexes
- Noxious stimuli evoke withdrawal reflexes

Bad

- Persistent depressed level of consciousness, absent brain stem reflexes
- Noxious stimulation evoked decortication or decerebration
- Eyes open with roving eye movements, uninhibited doll's eye movements or persistent vertical ocular deviation
- Spontaneous and evoked myoclonus
- Status epilepticus
- Persistently dilated pupils

MRI [25]

- Watershed infarcts of cortical and deep territories
- Cortical infarcts
- Blurring of grey and white junction
- Obliteration of the perimesencephalic cisterns with midbrain compression
- T2-weighted signal abnormalities of laminar necrosis

EEG [26]

- Diffuse slowing in the delta and theta range.
- Periodic lateralizing epileptiform discharges (PLEDs).
- Epileptiform activity.
- Alpha coma (bad prognostic sign) 9–12 cycles/second, transitory and does not vary with external stimuli and is seen in frontal and central parietal areas rather than in occipital distribution.

Hypertensive Encephalopathy and Reversible Posterior Leukoencephalopathy

Hypertensive encephalopathy is a manifestation of hypertensive emergency. Hypertensive emergency is defined as a severe elevation in blood pressure that precipitates end-organ damage. Examples of end-organ damage include acute pulmonary oedema, congestive heart failure, ischaemic chest pain, retinopathy, papilloedema, retinal haemorrhages, aortic dissection and acute renal failure [27, 28].

The concept of cerebral autoregulation explains the pathogenesis of these syndromes [29]. Experimental studies show that cerebral blood flow (CBF) remains constant over a wide range of cerebral perfusion pressure (CPP). If the intracranial pressure (ICP) does not change, the CPP reflects the mean arterial pressure (MAP) since $\text{CPP} = \text{MAP} - \text{ICP}$. Normotensive individuals autoregulate between a CPP of 50 mmHg and 150 mmHg. The ability to maintain a constant CBF despite changes in the CPP is mediated by changes in cerebrovascular resistance (CVR) ($\text{CBF} = \text{CPP} \div \text{CVR}$). As the blood pressure (and thus the CPP) increases, the intracranial vessels constrict. As the blood pressure (and CPP) decreases, the intracranial vessels dilate. If the upper limits of autoregulation are exceeded, hypertensive encephalopathy occurs; if the lower limits of autoregulation are exceeded, cerebral ischaemia ensues [29].

Patients with hypertensive encephalopathy most commonly present with headache, nausea, vomiting, visual obscuration, seizures and an alteration in the level of consciousness. The visual symptoms may range from a vague sense of visual blurring to cortical blindness [27–30]. Normal perfusion pressure breakthrough occurs in patients with severe carotid stenosis who undergo carotid endarterectomy and carotid stenting. In these patients, the cerebral hemisphere distal to the stenotic carotid is accustomed to receiving blood flow at very low pressures; the normal

autoregulatory set point is, therefore, lowered in the vascular territory fed by the carotid artery. Following endarterectomy, blood flow returns to the maximally dilated vascular bed at systemic pressures. When the ability to compensate for these high pressures is exceeded, a unilateral hypertensive encephalopathy occurs [31].

Imaging studies can help to corroborate the diagnosis of hypertensive encephalopathy. CT may show low-density changes in the posterior regions of the brain, but MRI is more sensitive and specific. Lesions are hyperintense on T₂ and fluid-attenuated inversion recovery-weighted images and hypointense on T₁-weighted images (Fig. 4.1). There is a predilection for involvement of the vertebrobasilar

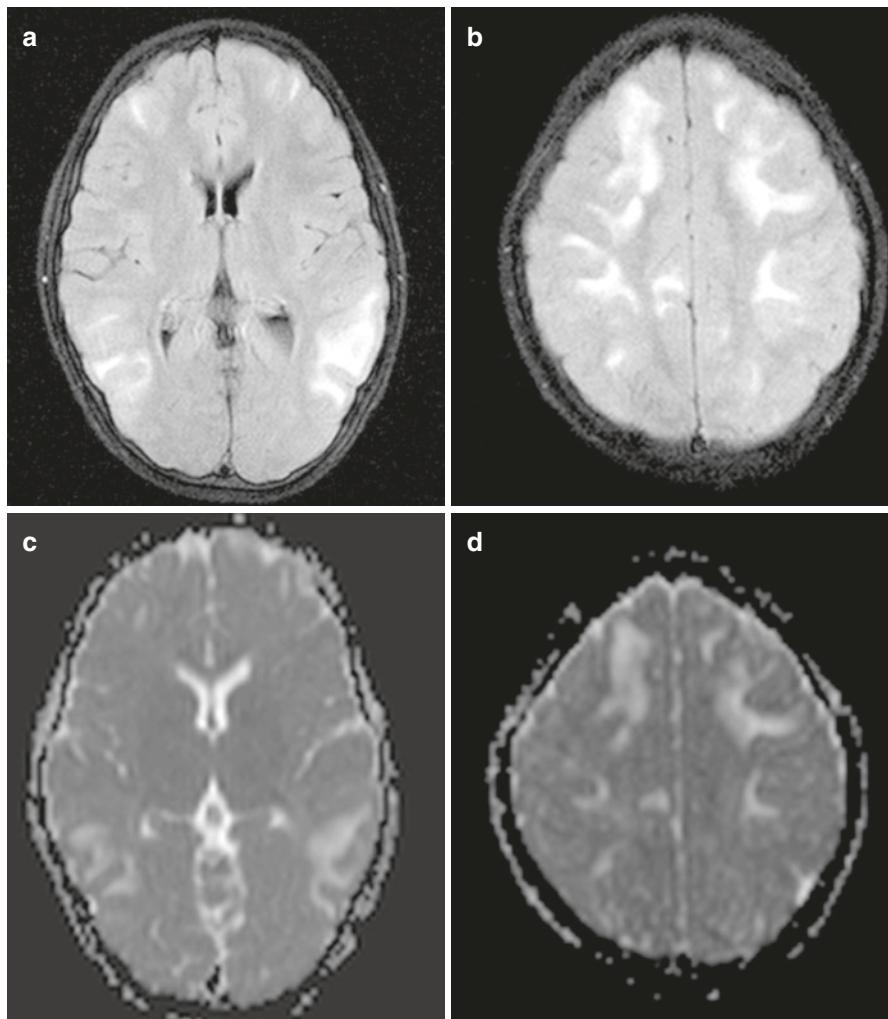


Fig. 4.1 MRI scan of the head in a patient with reversible leucoencephalopathy syndrome. FLAIR images (**a, b**) reveal hyperintensities posteriorly and also anteriorly. The same changes show increased diffusion on ADC (apparent diffusion coefficient) images (**c, d**)

circulation, with the occipital lobes and posterior parietal lobes being preferentially involved. The lesions are usually bilateral and symmetrical and follow the gyri in a serpentine manner; both white and grey matters are involved. The cerebellum and the brain stem may also get affected. In most cases, MRI abnormalities and the clinical symptoms resolve with treatment [32, 33]. The transient nature of these findings led to the terminology of reversible posterior leucoencephalopathy (RPLE) [34, 35]. However, the syndrome may not always be benign and the lesions may not always be reversible.

Determining whether a patient is symptomatic because of a hypertensive encephalopathy or is hypertensive because of acute stroke is extremely important because the therapeutic approach is very different for these two conditions. Cytotoxic oedema, which results from ischaemic brain injury, is bright on diffusion-weighted MRI (DWI); vasogenic oedema, which occurs in hypertensive encephalopathy, is not. The acute diffusion coefficient (ADC) map will show increased values in stroke. DWI with a matching ADC map is, therefore, quite useful for evaluating the hypertensive patient with focal neurological deficits [32]. The exact pathophysiology of hypertensive encephalopathy is unclear. The vulnerability of the tissue supplied by the posterior circulation may be related to the fact that the vertebral and basilar arteries do not receive as robust a sympathetic innervation as the blood vessels in the anterior circulation [31, 36].

Patients with hypertensive encephalopathy should be admitted to an intensive care unit. The best agents to use and the degree to which the blood pressure should be acutely reduced depends upon several variables, including the patient's pre-morbid blood pressure, the duration of his or her hypertensive emergency, concomitant medical disease and the extent of neurological involvement. It is generally recommended that the MAP be decreased by no more than 20–25% during the first 1–2 h with further reduction over the ensuing hours to days. The antihypertensive agents used to control blood pressure in hypertensive encephalopathy are given in Table 4.4.

Metabolic Coma [37–39]

Metabolic disorders often manifest as fluctuating levels of consciousness, agitation, delirium, certain motor phenomena, tremor, asterixis, multifocal myoclonus,

Table 4.4 Drugs given in hypertensive encephalopathy

Name	Onset of action	Duration	Dose	Precautions
Labetalol	5–10 min	3–6 h	10–20 mg i.v. may be repeated every 10 min	Heart block, failure
Sodium nitroprusside	Immediate	1–2 min	0.3/0.5 mcg/kg/min i.v.	ICP
Nitroglycerine	2–5 min	3–5 min	5 mcg/kg/min increments at 3–5 min	Headache
Enalaprilat	15–30 min	6 h	1.25 mg i.v. 6 hourly	Variable response

Some other drugs are hydralazine, diazoxide, nicardipine and esmolol

Table 4.5 The major metabolic causes of coma and their management

Disease	Coma	Mechanisms/features	Treatment
Hyponatraemia	Acute: <120 mEq%	Cytotoxic oedema	Hypertonic saline given cautiously to avoid central pontine myelinolysis (CPM)
Hypernatraemia	>155 mEq%	Dehydration, seizures	Slow rehydration
Hypoglycaemia	<30 mg%	Seizures, focal deficits	Urgent glucose bolus/infusion
Hyperglycaemia	Ketotic/non-ketotic	Hydration/acidosis	Slow correction
Hypoxia	PaO ₂ <40 mmHg	Loss of O ₂ for aerobic metabolism	Urgent correction
Renal failure	Variable	Acidosis	Dialysis
Hepatic failure	Variable	Brain ammonia Hyperventilation Decerebrate posturing	Treat cause, lactulose
Hypothyroidism	Chronic low levels	Myxoedema	Thyroid replacement

impaired remote memory or altered hallucinations. On general physical examination, one should check the vital signs, skin colour and breathing patterns and look for needle marks, cherry red discolouration of the lips and mucous membranes and abnormalities of the heart, lungs, liver and kidneys. Typically, metabolic encephalopathies spare pupillary reactions and ocular movements, with the important exception of Wernicke encephalopathy. The major metabolic causes of coma and their management are given in Table 4.5. Elderly patients are particularly vulnerable to the effects of metabolic insults and poorly tolerant of minor fluctuations in metabolic status. It is common to observe an elderly patient in coma due to relatively mild metabolic changes, whereas the same degree of changes in a healthy young individual may remain undetectable. For example, an elderly individual with minor urinary tract infection or pneumonia may become comatose. In fact, changes in the mental status of an elderly patient are often the first manifestations of sepsis.

In patients with coma suggesting metabolic dysfunction, the serum sodium, glucose, urea, creatinine, PaO₂ and PaCO₂ should be measured, and liver and thyroid function tests should be performed. A toxicology screen is mandatory if the cause is clinically unexplained. Sepsis can lead to coma, and evidence of infection should be sought in any delirious or comatose patient. Lumbar puncture must be performed for cerebrospinal fluid analysis in a patient with unexplained coma and a negative CT of the brain. Comas due to various metabolic factors have more similarities than differences.

Toxic Coma [40]

Coma secondary to drugs often resembles coma resulting from metabolic processes. However, respiratory suppression may be more common in patients with drug-induced coma than with metabolic coma. Similarly, some groups of drugs have

Table 4.6 Clinical features in common drug-induced coma

Drug type	Pupillary response	Other changes
Opioids	Pinpoint	None
Barbiturates	Reactive	None
Benzodiazepines	Reactive	None
Anticholinergics	Pupils dilated	Tachycardia, seizures
Anticholinesterases	Pupils constricted	Bradycardia, sweating, salivation
Cocaine/amphetamine	Pupils dilated	Tachycardia, hypertension, hypotension, arrhythmia
Neuroleptics	Pupils variable	Motor rigidity, hypotension, hyperthermia
Antidepressants	Pupils dilated	Rarely seizures

specific effects on the pupils. Physical findings in some of the more commonly diagnosed drug-induced comas are listed in Table 4.6.

A systematic approach to intoxications can be based on the recognition of certain toxicodromes, which can be helpful in limiting the number of diagnostic possibilities. These can be divided into autonomic toxicodromes, toxic temperature alterations and anion and osmolar gap disorders.

Autonomic Toxicodromes

Drugs that produce a sympathomimetic syndrome (cocaine, amphetamines, etc.) cause an increase in the heart rate, blood pressure and pupillary size, while the light reflex is preserved. The skin may be flushed or pale. Diaphoresis and fever may be noted. The gastrointestinal system may be hyperactive. The CNS manifestations include excitability, hallucinations and seizures, as well as coma. Drugs that produce the sympatholytic syndrome with reduced sympathetic nervous system activity include centrally acting α -2 agonists (clonidine, imidazole derivatives, opiates and some hypnotics in conjunction with ethanol). The anticholinergic syndrome reflects blocked sympathetic action. The clinical features include dilated and often fixed or unreactive pupils, mild tachycardia and hypertension, hypoactive bowel, urinary retention, dry skin and hyperthermia. The CNS complications of the anticholinergic syndrome include hallucinations, delirium, seizures or coma. The culprit drugs include cyclic antidepressants, antihistamines and anticholinergic agents. Some skeletal muscle relaxants and neuroleptic agents may also produce the anticholinergic syndrome. Organophosphates and so-called nerve gases, too, are implicated.

Toxic Temperature Alterations

Salicylates may produce hyperthermia, often combined with respiratory alkalosis, followed by metabolic acidosis. Seizures, coma and cardiovascular collapse may occur. The neuroleptic malignant syndrome is usually produced by neuroleptic agents with dopaminergic blocking activity, causing centrally mediated muscular

rigidity. Fever, muscular rigidity and variable confusion or delirium appears. The serotonin syndrome results from increased levels of serotonin at receptor sites. Agents that prevent the reuptake of inhibitors and some opioids that reduce serotonin metabolism are usually responsible. The clinical manifestations include confusion, ataxia, diarrhoea and excessive sweating. Hyperthermia, seizures and ventricular arrhythmias appear less commonly.

Anion and Osmolar Gap Disorders

The anion gap is calculated using the formula Anion gap = $\text{Na} - (\text{Cl} + \text{HCO}_3)$, with a normal value of 12–15 mmol/L. Anion gap acidosis is commonly produced by salicylates, methanol, ethylene glycol, iron, toluene and paraldehyde. Endogenous causes include diabetic ketoacidosis, uraemia and lactic acidosis. Patients present with coma and hyperventilation.

The term osmolar gap refers to the difference between measured osmolality and calculated osmolality, which is normally less than ten. Exogenous agents responsible for an increased osmolar gap include ethanol, isopropyl alcohol, acetone, methanol and ethylene glycol, the latter two are also responsible for a profound anion gap acidosis.

Temperature-Related Encephalopathy

It is important to consider the extremes of temperature, hyperthermia and hypothermia, in instances of coma with a negative CT scan. Hyperthermia may reflect difficulties with heat dissipation, excessive heat generation or hypothalamic dysfunction. Hypothermia results from a net loss of heat from the body, reflecting reduced metabolism, defective homeostatic mechanisms, exposure to cold or impaired vascular response. Hypothermia causes slowing of cerebral blood flow and in extreme cases, such vascular complications as disseminated intravascular coagulation. Coma usually appears at temperatures below 28 °C. When the core temperature is greater than 28 °C, one should look out for disorders such as sepsis, Wernicke encephalopathy, drug intoxication, hypothyroidism, shock and hypothalamic lesions.

Septic Encephalopathy [41, 42]

Sepsis-associated encephalopathy is a diffuse disturbance in cerebral function, appearing in the context of systemic inflammatory response. It is usually reversible, but in some advanced cases, there may be structural damage to the brain. There should be no evidence of direct CNS infection, head trauma, fat embolism and adverse reactions to antibiotics or sedatives. Mildly encephalopathic patients demonstrate a fluctuating confusional state and inappropriate behaviour. Inattention and

writing errors are common. More severely affected patients exhibit delirium, an agitated confusional state or coma. Prompt, specific treatment of the septic illness with prevention of multi-organ failure will diminish the mortality associated with sepsis. The administration of amino acids and branched chain amino acids has helped some patients with sepsis encephalopathy. Potential future therapies may target cytokine or free radical production, expression of cell adhesion molecules or nitric oxide generation.

Hashimoto Encephalopathy [43]

Hashimoto encephalopathy is a term used to describe an encephalopathy of presumed autoimmune origin, characterized by high titres of antithyroid peroxidase antibodies. Like autoimmune thyroid disease, Hashimoto encephalopathy is more common among women than men. It has been reported in paediatric, adult and elderly populations throughout the world. Hashimoto encephalopathy appears to be a rare disorder, but as it is responsive to treatment with corticosteroids, it must be considered in cases of ‘investigation-negative encephalopathies’. The clinical presentation may involve a relapsing and remitting course and include seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms and myoclonus. Thyroid function is usually clinically and biochemically normal. Despite the link to autoimmune thyroid disease, the aetiology of Hashimoto encephalopathy is unknown. It is likely that antithyroid antibodies are not pathogenic, but titres can be a marker of treatment response. More research is needed to further clarify the links between the clinical pictures, thyroid disease, autoantibody pattern and brain pathology. It may be that Hashimoto encephalopathy will be subsumed into a group of non-vasculitic autoimmune inflammatory meningoencephalopathies. This group may include disorders such as limbic encephalitis associated with voltage-gated potassium channel antibodies. Some authors have suggested abandoning any link to Hashimoto and renaming the condition ‘steroid-responsive encephalopathy associated with autoimmune thyroiditis’ (SREAT) to better reflect the current, if limited, understanding of this condition. The diagnosis is made in the first instance by excluding other toxic, metabolic and infectious causes of encephalopathy with neuroimaging and examination of the cerebrospinal fluid. Neuroimaging findings are often not helpful in clarifying the diagnosis.

When other toxic, metabolic and infectious causes are excluded, the common differential diagnoses are Creutzfeldt–Jakob disease, rapidly progressive dementias and paraneoplastic and non-paraneoplastic limbic encephalitides. In the context of the typical clinical picture, high titres of antithyroid antibodies, in particular anti-thyroid peroxidase antibodies, are diagnostic. However, these antibodies can also be detected in elevated titres in the healthy general population. Treatment with corticosteroids is almost always successful, although relapse may occur if this treatment is ceased abruptly. Other forms of immunomodulation, such as intravenous immunoglobulin and plasma exchange, may also be effective.

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Fever with Altered Sensorium

5

Manish Modi, Sudesh Prabhakar, and Praveen Sharma

Introduction

Any patient presenting in altered sensorium poses a diagnostic and therapeutic challenge for the treating physician. With the advent of increasing number of non-infectious causes, especially autoimmune encephalitis, the diagnostic work-up of patient with encephalopathy is ever growing and so are the management options. Recently many antibodies against intracellular antigens, synaptic receptors, ion channels and other cell surface proteins have been recognized in association with wide variety of autoimmune encephalitic syndromes, which has further complicated the work-up of patients of febrile encephalopathy. The timely recognition of these non-infectious syndromes is equally important as aggressive immunosuppression can prevent long-term sequelae [1–5].

A patient with fever and altered sensorium constitutes a medical emergency. Early recognition of the condition, efficient decision-making and rapid institution of therapy can be life-saving. The presence of fever in itself is not sufficient to make a diagnosis of an infective aetiology (such as meningitis or encephalitis). Moreover, encephalopathy may be precipitated by systemic infections or sepsis without cerebral inflammation (septic encephalopathy) [1]. Sepsis can lead to altered sensorium secondary to systemic complications such as hypoglycaemia, hypovolaemia, hyperpyrexia and hepatic or renal failure [1]. Even in the absence of infection, there can be an uncontrolled rise in body temperature due to mechanisms, such as overproduction of heat or impaired dissipation of heat, or due to non-infective CNS diseases

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or hypothalamic lesions [2]. Patients with neuroleptic malignant syndrome (NMS) have fever, altered sensorium and neck stiffness, along with generalized rigidity, even after the offending drug has been withdrawn, and NMS constitutes an important differential diagnosis of acute encephalitis [3]. Table 5.1 summarizes some common and important causes of altered sensorium with fever. In many cases, the presence of focal neurological signs and focal seizures distinguishes encephalitis from encephalopathy. However, it may not be possible to make this distinction on clinical grounds alone, and other investigations, such as cerebrospinal fluid (CSF) analysis and imaging, are usually required to rule out an infective aetiology [4, 5]. Figure 5.1 outlines the systematic approach to a patient who presents to the emergency department with fever and altered sensorium.

Table 5.1 Causes of fever with altered sensorium

A. Infections

- Encephalitis
- Meningitis
- Cerebral malaria
- Brain abscess, subdural or epidural empyema
- Sepsis-associated encephalopathy (SAE)
- Sepsis with disseminated intravascular coagulation/thrombotic thrombocytic purpura (DIC/TTP)

B. Non-infectious causes of fever

Overproduction of heat

- Neuroleptic malignant syndrome (NMS)
- Malignant hyperthermia
- Serotonin syndrome
- Cocaine, amphetamine toxicity
- Ecstasy intoxication
- Salicylate poisoning
- Thyrotoxic encephalopathy
- Convulsive status epilepticus
- Catatonic schizophrenia

Impaired heat dissipation

- Anticholinergic toxicity, e.g. amitriptyline
- Heat stroke

Structural lesions (impaired thermoregulatory mechanism)

- Hypothalamic lesion
- Brainstem lesions (stroke)
- Intraventricular and subarachnoid haemorrhage
- Vasculitis, e.g. systemic lupus erythematosus

Miscellaneous

- Infectious or postinfectious demyelination (ADEM)
- Cerebral fat embolism
- Altered sensorium with secondary cause of fever, e.g. stroke with aspiration pneumonia
- Primary CNS or metastatic malignancies

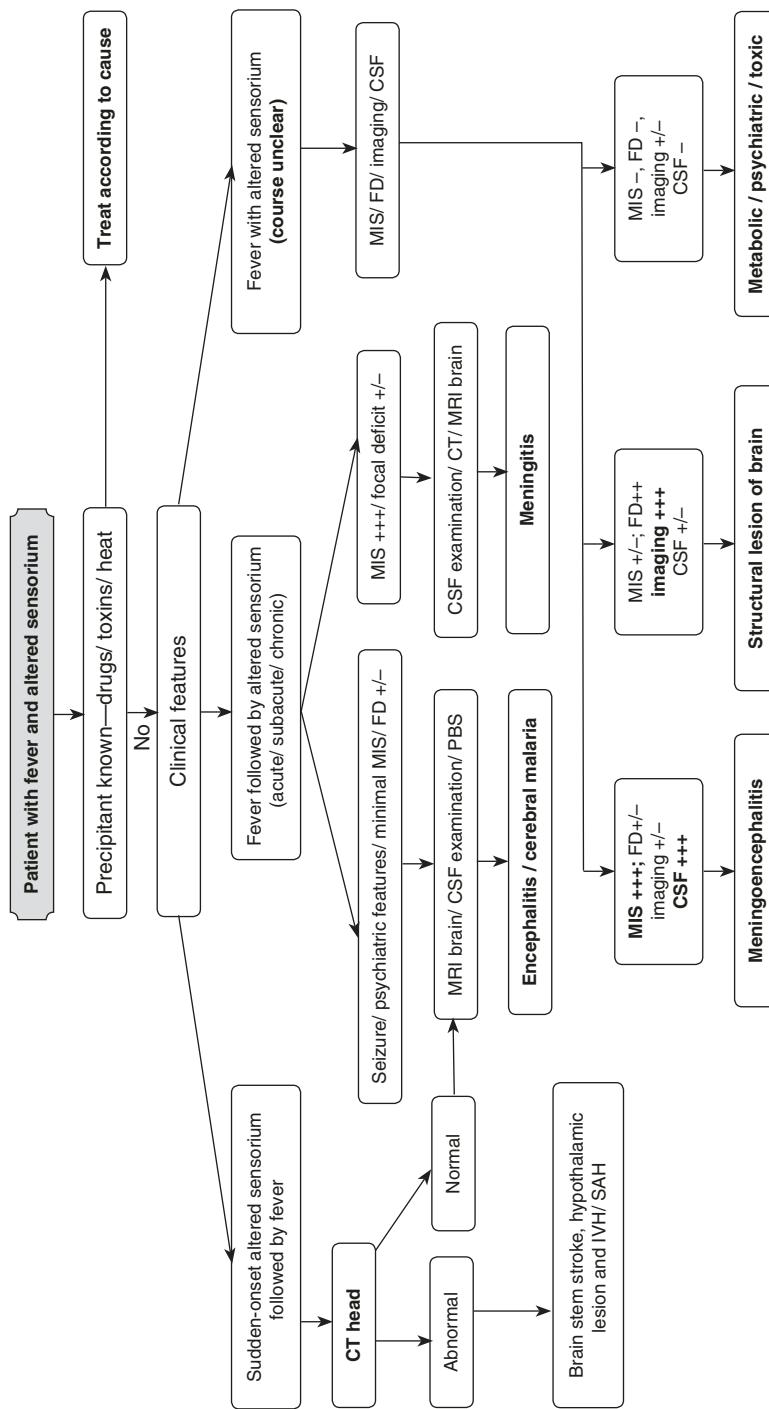


Fig. 5.1 Algorithmic approach to a patient with fever and altered sensorium. *MIS* meningeal irritation signs, *FD* focal deficits, *CSF* cerebrospinal fluid, *CT* computed tomography, *MRI* magnetic resonance imaging, *IVH/SAH* intraventricular/subarachnoid haemorrhage, *PBS* peripheral blood smear

The diagnosis of acute infective meningoencephalitis is suspected in a febrile patient who presents with altered consciousness and signs of diffuse cerebral dysfunction [1]. Worldwide, infection of the CNS is the commonest cause of fever with altered sensorium [1, 5, 6] (Table 5.2). In a study from India among children <18 years of age, the commonest cause of acute febrile encephalopathy was viral encephalitis, which accounted for around 40% of the cases. Among the non-viral causes, bacterial meningitis (33.8%), tubercular meningitis (7.9%) and cerebral malaria (5.2%) were the most common [7]. Herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), mumps, measles and enteroviruses are responsible for most cases of acute viral encephalitis among immunocompetent individuals in the United Kingdom [1].

The distinct clinical syndromes related to infections of the CNS include acute bacterial meningitis, viral meningitis, encephalitis and brain abscess [6]. Each of these syndromes initially presents with a non-specific prodrome of fever and headache, until altered sensorium, focal deficits or seizures appear. Some non-infectious or immune-mediated encephalitic syndromes, which mimic viral encephalitis, have been increasingly recognized in up to one-third of cases of febrile encephalopathy and are enumerated in Table 5.3. This chapter focuses on a systematic approach to a patient with febrile encephalopathy, with an emphasis on the findings of the history and physical examination, interpretation of CSF results, role and timing of imaging studies and other modalities of investigation (Fig. 5.1).

Table 5.2 Causes of infectious meningoencephalitis

Viral

DNA viruses: Herpes simplex virus (HSV1, HSV2), other herpes viruses (HHV6, EBV, VZV, cytomegalovirus) and adenovirus (e.g. serotypes 1, 6, 7, 12, 32)

RNA viruses: Influenza virus (serotype A), enterovirus, poliovirus, measles, rubella, mumps, rabies, arboviruses (e.g. Japanese B encephalitis, St Louis encephalitis virus, West Nile encephalitis virus, eastern, Western equine encephalitis viruses), reovirus (Colorado tick fever virus) and retrovirus (HIV)

Bacterial

Bacterial (pyogenic) meningitis, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Listeria monocytogenes*, *Borrelia burgdorferi* (Lyme disease), *Tropheryma whippleii* (Whipple disease), *Leptospira*, *Brucella* (particularly *Brucella melitensis*), *Legionella*, *Salmonella typhi* (typhoid fever)

Rickettsial

Rickettsia rickettsii (Rocky Mountain spotted fever), *Rickettsia typhi* (endemic typhus), *Rickettsia prowazekii* (epidemic typhus), *Coxiella burnetii* (Q fever)

Fungal

Cryptococcosis, coccidioidomycosis, histoplasmosis, blastomycosis, candidiasis

Parasitic

Plasmodium, *Trypanosoma*, *Toxoplasma gondii*, *Naegleria fowleri*, *Schistosoma*

Table 5.3 Important immune-mediated encephalitis**ADEM (acute disseminated encephalomyelitis)**

Acute disseminated encephalomyelitis is an inflammatory, multifocal, demyelinating condition characterized by multifocal neurological deficits, seizures and altered sensorium.

Approximately one-fourth of patients have serum antibodies to myelin oligodendrocyte glycoprotein (MOG). Typically MRI reveals multiple lesions in subcortical, central and periventricular white matter and deep grey matter. Acute haemorrhagic leukoencephalopathy (AHLE) is a rare, hyperacute form of ADEM that overlaps with cerebral vasculitis.

Anti-NMDA receptor encephalitis

Anti-N-methyl-D-aspartate receptor encephalitis typically presents with psychiatric symptoms, seizures, memory loss and later on altered sensorium. There can be movement disorders (orofacial limb and trunk dyskinesias), abnormal posturing and dysautonomia. It is usually associated with ovarian teratoma in young females less than 45 years of age and with carcinomas in adults above 45 years. Diagnosis is confirmed by IgG antiGlu-N1 antibodies in CSF.

Limbic encephalitis

'Limbic encephalitis' occurring in adults is often associated with malignancy. The encephalitis may occur prior to the diagnosis or during the course of cancer treatment. The tumours most often associated with limbic encephalitis are small-cell lung carcinomas (SCLC), testicular germ cell tumours, breast cancer, ovarian teratoma, Hodgkin lymphoma and thymoma. The most commonly identified antibodies in this group are against intracellular neuronal antigens: Anti-Hu, anti-Ma2(ta), anti-V2/CRMP5, anti-amphiphysin and anti-voltage-gated potassium channel-complex (anti-VGKC). Treatment is directed towards the underlying tumour; immunomodulatory treatments are often used adjunctively.

Bickerstaff's brainstem encephalitis

Bickerstaff's brainstem encephalitis is characterized by subacute onset, in less than 4 weeks, of progressive impairment of consciousness along with ataxia and bilateral, mostly symmetrical, ophthalmoparesis. Patients frequently develop pupillary abnormalities, bilateral facial palsy, Babinski's sign and bulbar palsy. Generalized limb weakness can occur, which overlaps with features of Guillain-Barre syndrome. Brain MRI is usually normal, but brainstem abnormalities on T2-weighted FLAIR imaging are present in 23% of patients. IgG anti-GQ1b antibodies are highly specific for this disorder.

Approach to the Patient

History

The patient's history may hold the most important and sometimes the only clue to a correct diagnosis. A careful and systematic clinical assessment based on positive evidence, and not exclusion, is key to the management of a patient with febrile encephalopathy [4]. At the outset, it is important to differentiate infective from non-infective causes of altered sensorium, because infection mandates prompt empirical antimicrobial therapy (Fig. 5.2). The temporal course of the illness is important, and it should be ascertained whether the fever preceded or followed altered sensorium

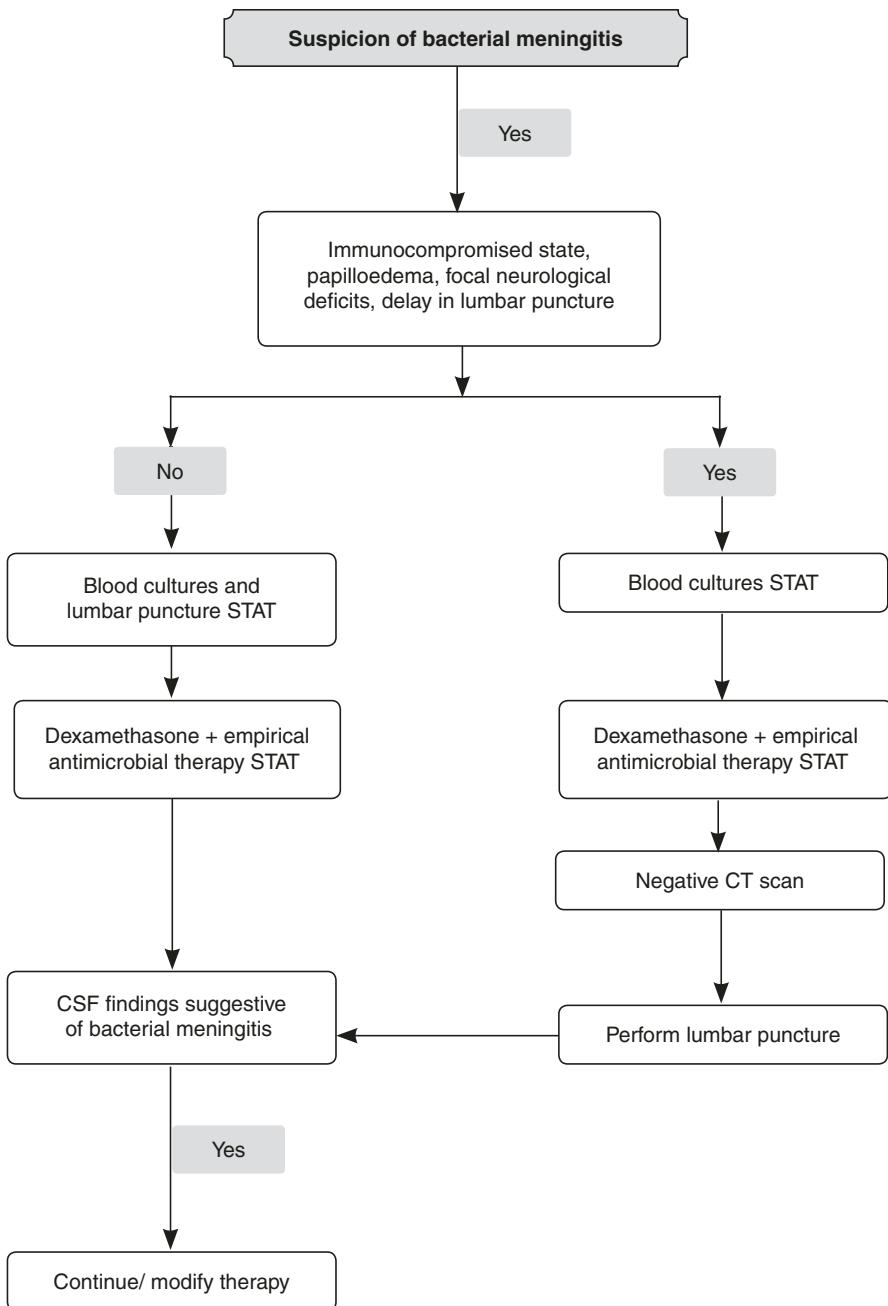


Fig. 5.2 Management algorithm for suspected bacterial meningitis

or occurred simultaneously. The clinical hallmarks of CNS infection are fever, headache and altered mental status. In one study, the historical ‘classic triad’ of fever, stiff neck and altered mental status was found in two-thirds of 493 episodes of bacterial meningitis in adults [8]. At least one of the elements of the triad was found in all patients, and the non-specific finding of fever was the most common feature [8]. A pooled meta-analysis of 11 studies involving 845 patients reported that the classic triad was observed in 46% of patients with meningitis, but 99% had at least one feature [9].

These findings illustrate the difficulty faced by emergency physicians, as many cases of bacterial meningitis lack the typical constellation of findings that would distinguish this infrequent life-threatening diagnosis from more common and benign conditions.⁴ Moreover, the sensitivity of all these symptoms reduces further in children, who cannot verbalize their symptoms. Seizure is considered to be an important symptom of meningitis in children, but not as a sole manifestation, and is usually associated with other findings, such as persistent altered sensorium or nuchal rigidity. Hence, children older than 2 months with simple febrile seizures whose mental status clears quickly and who have no other signs of CNS infection can be safely discharged home on antipyretics without lumbar puncture, after age-appropriate work-up for the febrile illness [10].

If the symptoms point towards an infective cause of febrile encephalopathy, the history should also focus on conditions that may increase a patient’s risk of contracting an infection, such as asplenia, prosthetic devices, HIV status and other immune deficiency states such as those caused by diabetes, immunosuppressive drugs, steroids and chemotherapy and/or radiotherapy. This is because immunosuppressed individuals are more prone to certain infections, such as listeriosis, cryptococcosis and cytomegalovirus.

It is essential to always find out whether the patient has recently been abroad, suffered insect or animal bites or possibly had contact with individuals suffering from infectious diseases. Both the geographical distribution and seasonal occurrence may offer important clues [1, 4, 5]. Japanese encephalitis is endemic in Asian countries and peaks in the rainy season [1, 11]. Cerebral malaria, a potentially fatal complication of *Plasmodium falciparum*, is the most important cause of unarousable coma in febrile patients in endemic areas. The mode of onset and progression of the illness also provide a valuable clue to the aetiology. A subacute-to-chronic course over days to weeks favours a tubercular or cryptococcal aetiology, while rapid worsening favours acute meningitis, encephalitis and, among the non-infectious causes, drug overdose or a subarachnoid haemorrhage. Among the common differential diagnoses in an acutely febrile and confused trauma patient is cerebral fat embolism [12]. It is important to take a history of drug intake, with special reference to neuroleptics, cocaine, ecstasy and amphetamines. Table 5.4 enumerates the important points that need to be clarified while taking the medical history.

Table 5.4 History—important points

- Onset of altered sensorium
- Headache
- Fever—grade/type
- Joint pains/rashes
- Nausea and vomiting
- Contact with animals/dog bite
- Tick/mosquito bite
- Seizures
- Focal deficit
- Geographical area
- Recent travel
- Drug addiction/use of antipsychotics
- Co-morbid illness such as diabetes
- Treatment with immunosuppressants/chemotherapy
- Recent illness/surgery
- Trauma
- Fresh water drowning/mud exposure

Table 5.5 Physical signs in suspected meningitis

Kernig sign	Flexing the hip and extending the knee to elicit pain in the back and legs
Brudzinski sign	Passive flexion of the neck elicits flexion of the hip
Nuchal rigidity	Severe neck stiffness
Jolt accentuation	Exacerbation of existing headache with rapid head rotation

Physical Examination in a Patient with Fever and Altered Sensorium

Stiffness of the neck, altered mental status and fever are the classical findings in a patient with suspected meningitis or meningoencephalitis. The sensitivity of these signs has been found to be 70%, 67% and 85%, respectively, in a meta-analysis [13]. The classical signs of meningeal irritation in a patient with meningitis are elaborated in Table 5.5.

A thorough general physical examination and neurological examination can provide important clues to the underlying cause. The identification of concomitant pneumonia, diarrhoea and skin or bone lesions may offer clues to the aetiology. Skin rashes are common in meningococcal infection, rickettsial fever, VZV, Colorado tick fever, etc. Parotitis occurs with mumps, and erythema nodosum may be associated with tuberculosis and histoplasmosis. Mucous membrane lesions are common in herpes virus infection. Upper respiratory tract infection may favour influenza and mycoplasma. In addition, a thorough examination should be carried out to look for lymphadenopathy, hepatosplenomegaly, etc. [1, 4–6]

A detailed neurological examination, including checking the pupillary size and reaction as well as forced eye deviation, looking for evidence of any cranial nerve involvement, abnormal movements, decerebrate rigidity or focal neurological deficits, fundus examination for papilloedema, etc., helps in diagnosis and planning investigations. In one study, it was found that loss of the pupillary light reflex and

Table 5.6 Evaluation of a patient with febrile encephalopathy**History**

- Fever, headache, vomiting, altered sensorium
- Geographical and seasonal factors
- Immune status, drug intake
- Contact with animals, dog bite, insect bite
- Foreign travel
- Occupation
- Psychosis, cognitive impairment
- Movement disorder

Clinical signs

- Fever, neck stiffness, altered sensorium Cranial nerve palsies
- Kernig sign, Brudzinski sign, jolt accentuation
- Skin and mucous membranes; rash
- Lymph nodes, liver, spleen
- Other sites of concomitant infection
- Neurological examination including fundus for papilloedema, cranial nerve involvement, focal deficits, brainstem signs, autonomic signs

Investigations

- Blood: Including total and differential leukocyte count, coagulation profile, blood cultures, biochemistry, arterial blood gases
- Urine analysis, including myoglobinuria
- Chest X-ray
- Lumbar puncture: With detailed CSF analysis
- Neuroimaging
- EEG

In selected cases

- Thyroid function test
- Drug levels
- Urine toxicology screen

anisocoria were both independently associated with a structural cause of coma, although anisocoria was found to be more specific [14]. The commonly reported focal abnormalities are hemiparesis, aphasia, ataxia, pyramidal signs, cranial nerve deficits, involuntary movements (myoclonus and tremors), partial seizures and papilloedema. The presence of these signs may warrant neuroimaging before lumbar puncture in some situations. After getting clues from the history and examination, investigations are tailored as per the provisional diagnosis (Table 5.6) [1, 4–6, 15].

Investigations

Blood Investigations

All patients of fever with altered sensorium should undergo blood cultures. Blood cultures are positive in 30–80% of cases of bacterial meningitis [10, 16, 17]. Relative lymphocytosis in the peripheral blood is common in viral encephalitis. Leukopenia

and thrombocytopenia are characteristic of rickettsial infections and viral haemorrhagic fevers. A peripheral blood film is the most sensitive and specific test for cerebral malaria [18].

Chest Radiography

A chest X-ray is also advisable in all patients with febrile encephalopathy and may reveal changes suggestive of infections such as mycoplasmosis, legionellosis or tuberculosis [1].

Lumbar Puncture

Lumbar puncture (LP) is indicated in almost all patients with fever and altered sensorium where the index of suspicion for meningitis or encephalitis is high. Certain reports have emphasized the risk of brain herniation as a complication of diagnostic lumbar puncture. Table 5.7 summarizes the guidelines for adult patients who should undergo computed tomography (CT) scan before a lumbar puncture [19].

Studies routinely obtained at the time of lumbar puncture include the measurement of CSF pressure, gross examination for turbidity, checking for change in colour, measurement of CSF protein and sugar concentrations, cell count, Gram stain, India ink stain and fluid culture for bacteria, mycobacterium and fungus. On an average, 15–20 mL of CSF is required for routine analysis, and another 5–10 mL may be required for special tests [20]. The CSF findings in normal and abnormal conditions are summarized in Table 5.8, and those in various meningoencephalitides are given in Table 5.9. Depending on the clinical suspicion, the CSF can also be analysed for special investigations as given in Tables 5.10 and 5.11.

Table 5.7 Recommended criteria for adult patients with suspected bacterial meningitis, who should undergo CT scan before lumbar puncture [19]

Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy or after transplantation
History of CNS disease	Mass lesion, stroke or focal infection
New-onset seizure	Within 1 week of presentation, some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures
Papilloedema	Presence of venous pulsations suggests absence of increased intracranial pressure
Abnormal level of consciousness	Moderate-to-severe impairment of consciousness Glasgow Coma Scale (GCS <10)
Focal neurological deficit	Dilated non-reactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift

Table 5.8 Cerebrospinal fluid examination (normal and abnormal conditions)

CSF tests	Normal	Abnormal	Causes
Opening pressure	60–180 mmH ₂ O ^a	<60 mmH ₂ O >200 mmH ₂ O	CSF leak Infection, stroke, intracranial tumours, IIH, CVT, SAH
Colour	Crystal clear	Xanthochromic Turbid Green Pink Orange	Hyperbilirubinaemia: CSF protein >150 mg% >200 WBCs Hyperbilirubinaemia: Purulent CSF Blood breakdown products: Traumatic CSF tap Carotinaemia, blood breakdown products
Total cell count	≤5	>5 (depends upon condition and may range from ten to thousands)	Meningitis, encephalitis, non-infectious inflammatory diseases, post-seizure, ICH, malignancy, traumatic
Differential cell count	70% lymphocytes 30% monocytes occasionally single polymorph or eosinophil	Lymphocytes predominant PMNs predominant Eosinophilic (>10 eosinophils/cmm field or >10% of total cells)	Viral, tubercular, fungal meningitis Bacterial meningitis Parasitic; uncommonly viral, fungal and rickettsial meningoencephalitides
Protein	15–50 mg%	<15 mg% >50 mg%	Children <2 years of age, CSF leak, acute water intoxication, IIH (few cases) CNS infections, tumours, ICH, demyelination, some endocrine disorders (myxoedema)
Glucose	45–80 mg% or 2/ third of plasma glucose (CSF-to-plasma glucose ratio 0.6–0.7)	<35 mg% or <2/third of plasma glucose in normoglycaemic conditions ^b	AIDP, CIDP, a few metabolic disorders Infectious meningitis, encephalitis, chemical meningitis, SAH

Microscopy

Gram stain	–	+ve	90% untreated bacterial meningitis (depends on causative organism also) 40–60% partially treated bacterial meningitis
AFB stain	–	+ve	Tubercular meningitis (37%)
India ink	–	+ve	Cryptococcal meningitis (50% cases)
Giemsa	–	+ve	Special stain used to detect toxoplasma

^aOpening pressure is low (10–100 mmH₂O) in young children <8 years of age

^bNormal CSF glucose does not rule out infection as it is normal in most of the viral meningoencephalitides and may be normal in 50% cases of bacterial meningitis

H₂O water, CSF cerebrospinal fluid, IIH idiopathic intracranial hypertension, SAH subarachnoid haemorrhage, WBCs white blood cells, ICH intracerebral haemorrhage, PMNs polymorphonuclear cells, AIDP acute inflammatory demyelinating polyradiculoneuropathy, CIDP chronic inflammatory demyelinating polyradiculoneuropathy, AFB acid-fast bacilli

Table 5.9 CSF picture in various meningitides

Tests	Viral	Bacterial	Tubercular	Fungal
Opening pressure	Usually normal	Elevated	Elevated/variable	Elevated/variable
Colour	Normal	Turbid	Xanthochromic/variable	Clear/variable
Total cells	<100/cmm	>1000/cmm	Variable (100–500/cmm)	Variable
Differential ^a	Lymphocytic	Polymorphonuclear	Lymphocytic	Lymphocytic
Protein	Normal to elevated	Elevated	Elevated	Elevated
Glucose	Usually normal	Decreased	Decreased	Decreased

^aEarly stages of viral, tubercular and fungal meningitis may show polymorphonuclear leukocytosis and early stages of bacterial meningitis may show lymphocytic predominance

Table 5.10 Rapid CSF tests for determination of bacterial aetiology

Gram stain	Sensitivity of this test varies 50% to 90% but decreases to 7–41% among patients taking oral antibiotics [8, 10]. Concentration of $\leq 10^3$ colony forming units (CFU)/mL is associated with a positive Gram stain result 25% of the time; 10^3 – 10^5 CFU/mL yield a positive Gram stain result in 60% and $>10^5$ CFU/mL lead to positive results in 97% of cases [14]
Latex agglutination	The sensitivity of this test varies from 78% to 100% for <i>H. influenzae</i> , 67–100% for <i>S. pneumoniae</i> , 69–100% for <i>Streptococcus</i> and 50–93% for <i>N. meningitidis</i> . Latex agglutination may be most useful for the patient who has been pretreated with antimicrobial therapy and whose gram stain and CSF culture results are negative [15, 21]
Limulus lysate assay	It detects $\sim 10^3$ gram-negative bacteria/mL of CSF and as little as 0.1 ng/mL of endotoxin [15, 21]
PCR	Sensitivity of 100%, specificity of 98.2%, a positive predictive value of 98.2% and negative predictive value of 100% [15, 22]

Table 5.11 Laboratory tests helpful in distinguishing bacterial from viral meningitis

CSF lactate level	CSF lactate concentration of >4.2 mmol/L is considered to be a positive discriminating factor for bacterial meningitis, with a sensitivity of 96% and specificity of 100%. It is valuable in the subgroup of postoperative neurosurgical patients, in which empirical antimicrobial therapy should be considered if CSF lactate concentrations are >4.0 mmol/L, pending results of additional studies [15, 23, 24]
CRP concentration	Serum CRP concentration is capable of distinguishing gram stain-negative bacterial meningitis with a sensitivity of 96%, a specificity of 93% and a negative predictive value of 99%. A normal CRP has a high negative predictive value in the diagnosis of bacterial meningitis [15, 25, 26]
Procalcitonin concentration	In children, the sensitivity of procalcitonin levels (>5 µg/L) for diagnosis of bacterial meningitis was 94%, and the specificity was 100%, while in adults, serum concentration > 0.2 µg/mL had a sensitivity and specificity of up to 100% for diagnosis of bacterial meningitis [15, 27–29]
PCR	Viral testing using PCR is another modality to identify patients with aseptic meningitis, especially enterovirus [15, 30]

The Bacterial Meningitis Score has been recently validated in a multicentre retrospective cohort study of 2903 children with CSF pleocytosis. In this study, 121 (4.2%) were found to have bacterial meningitis, and the absence of all five variables (one point each) included in the scoring system (i.e. positive Gram stain, CSF WBC >1000 cells/mL, CSF protein >80 mg/dL, peripheral blood absolute neutrophil count >10,000 cells/mL and history of seizure before presentation) had a negative predictive value of 99.9% for bacterial meningitis. A score of 1 or more identified all children older than 2 months with this disease [31].

Neuroimaging

Brain imaging is frequently an essential part of the evaluation of the patient. Although a magnetic resonance imaging (MRI) scan would be ideal, it may be simpler to obtain a cranial CT scan in a sick patient. As already discussed, there are certain situations in which an urgent CT scan is required to rule out a mass lesion or an abscess before performing lumbar puncture [19]. Characteristic neuroimaging changes may also offer clues to the specific infective aetiologies, for example, frontotemporal changes in herpes simplex encephalitis (HSE), thalamic and mid-brain changes in Japanese encephalitis and disseminated lesions in brainstem and basal ganglia in Eastern equine encephalitis [1, 4–6, 12, 32]. The presence of basal exudates after the administration of contrast is suggestive of tubercular meningitis. Predominant basal ganglia ring-enhancing lesions may suggest toxoplasmosis in an immune-compromised individual, and multiple ring-enhancing lesions in a patient with chronic meningitis favour tuberculomas [1, 4, 32]. Table 5.12 enumerates some important features on MRI, which points towards certain clinical syndromes [33–37].

Table 5.12 MRI features helpful in differentiation of underlying aetiology

- Brainstem: Enteroviruses (esp. EV71), JEV, WNV, Nipah, *B. pseudomallei*, *L. monocytogenes*, anti-NMO (anti-AQP4), anti-Hu, anti-ma
- ‘Limbic’: HSV, HHV6, anti-NMDAR, anti-VGKC, anti-GAD, anti-Hu, anti-ma
- Cerebellum: EBV, VZV, enteroviruses, *M. pneumoniae*
- Subcortical grey matter: EBV, flaviviruses (esp. JEV), influenza, MTB, post-streptococcal, *M. pneumoniae*, anti-DR2
- Frontal lobe: *N. fowleri*, *B. mandrillaris*
- ‘Vasculitic’: VZV, systemic lupus erythematosus (SLE) and other cerebral vasculitides
- Multifocal white matter lesions: ADEM, JCV-PML

ADEM acute disseminated encephalomyelitis, DR2 dopamine-2 receptor, EBV Epstein–Barr virus, GAD glutamic acid decarboxylase, HHV6 human herpes virus-6, HSV herpes simplex virus, JCV John Cunningham virus, JEV Japanese encephalitis virus, MTB *Mycobacterium tuberculosis*, NMDAR N-methyl-D-aspartate receptor, NMO neuromyelitis optica (AQP4, aquaporin-4), VGKC voltage-gated potassium channel, VZV varicella zoster virus, WNV West Nile virus

Electroencephalogram (EEG)

EEG is important in a patient with febrile encephalopathy to rule out a non-convulsive status. Although not very specific, EEG is recommended in any suspected case of acute encephalitis since it may help in distinguishing focal encephalitis from generalized encephalopathy. In the latter, the EEG may show diffuse, bihemispheric slowing, for example, triphasic slow waves in a case of hepatic encephalopathy. The EEG is invariably abnormal in HSE and evolves from a non-specific slowing to more characteristic 2–3 Hz, periodic lateralized epileptiform discharges originating from the temporal lobes. This finding is limited to about half the cases in the later stages [1, 4, 6, 15].

Conclusion

The diagnostic approach to a patient presenting with fever and altered sensorium poses a real challenge, especially when the history is not reliable. However, in all cases of an acute febrile encephalopathy, a systematic approach to the history, examination and investigations forms an integral part of the management strategy.

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Raised Intracranial Pressure

6

Manish Singh Sharma

Introduction

Raised intracranial pressure (ICP) is one of the foremost critical-care emergencies that a neurological health specialist can be called upon to recognize and treat.

ICP is defined, quite simply, as arterial pressure within the skull, which is damped by the brain, cerebrospinal fluid (CSF) and the meninges. Most of our knowledge about ICP comes from studying patients with traumatic brain injuries, details of which can be found in the *Edwin Smith Papyrus* (1650–1550 BC) [1]. Hippocrates of Kos (460–377 BC), the ancient Greek physician widely hailed as the ‘father of medicine’, in his collection of salvaged works published under the title *Corpus Hippocraticum*, advocated trephining for fissured, contused and dented fractures with contusion to create an opening for excess blood and CSF [2, 3]. Hippocrates may also have been the first to perform ventricular punctures for hydrocephalus [2]. The concept of ICP was probably elaborated for the first time by Alexander Monro (1733–1817), a Scottish physician at the University of Edinburgh, and by his pupil George Kellie [4, 5]. A dilated non-reactive pupil in an unconscious patient on the side of an intracranial mass lesion secondary to a paralysis of the oculomotor nerve is probably the single most important sign associated with an acute episode of raised ICP. This eponymous sign was named after Sir Jonathan Hutchinson (1828–1913), an English surgeon, ophthalmologist, dermatologist, venereologist and pathologist. Quincke, in 1911, first described lumbar puncture to relieve brain pressure [6]. The importance of monitoring ICP was broadly recognized only in the late 1960s when Lundberg, developing on the earlier works of Guillaume and Janny (1951), published his findings [7, 8].

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ICP is also synonymous with CSF pressure. It can also be defined as the pressure that must be exerted against a needle introduced into the CSF space to prevent its escape. This is a tightly regulated parameter with a pressure that varies between 5 and 10 mmHg in adults and older children in the supine lateral position. The upper limit of normal would be considered as 15 mmHg, but transient increases up to 30–50 mmHg have been noticed after sneezing or coughing [9]. ICP can also be measured in mmH₂O—the conversion factor being 13.6 (the relative density of Hg). The SI unit of pressure is the pascal (Pa). One kilo Pa is 7.5 or 102 mmH₂O [9]. Intracranial hypertension is said to exist at ICP values exceeding 20 mmHg.

Physiology

The Monro–Kellie Doctrine

Central to understanding the concept of ICP is the ‘Monro–Kellie’ doctrine, which is based on the principle that the skull is a rigid closed box and that the brain is virtually incompressible. Thus, the volume of brain matter, CSF and intracranial blood is a constant [4, 5]. Any increase in one is compensated by a decrease in the volume of the other two. As and when a pathological fourth space begins to accumulate, the first compartment to compensate is the CSF, which shifts to the intraspinal subarachnoid space. Venous blood follows and as the ICP rises, cerebral perfusion pressure (CPP) (CPP = mean arterial pressure [MAP]—ICP; MAP = diastolic blood pressure [BP] + 1/3 pulse pressure) drops, affecting arterial blood supply. This reflects in a loss of consciousness.

CSF Dynamics

The volume of the adult skull is 1500 mL, 87% of which is occupied by the brain, 9% by the CSF and 4% by blood [10]. Mean cranial CSF volume is 164.5 mL (range 62.2–267 mL), whereas mean ventricular volume is 31.9 mL (range 7.49–70.5 mL) [11]. Draining the intracranial CSF is thus the most ‘physiologically effective’ method of treating ICH. Ventricular catheters introduced within the skull to drain the CSF are considered to be the gold standard, as they can also be connected to manometers to measure global ICP values.

Cerebral Blood Volume (CBV), Blood Flow and Pressure Autoregulation

CBV is essentially linked to cerebral blood flow (CBF), which is influenced largely by the ICP, the intracranial arteriovenous pressure gradient and cerebrovascular resistance. The last two variables are in turn determined by the diameter of the vessel. Mean normal adult CBF is 53 mL/100 g/min and is tightly maintained by a poorly understood phenomenon known as cerebral pressure autoregulation, despite

a wide fluctuation in the CPP from 50 to 150 mmHg. Pressure autoregulation is likely to be a local response of blood vessels to changes in luminal pressure, which result in vasoconstriction as the CPP rises and vasodilatation as it falls, thereby maintaining the CBF. Beyond the lower (50 mmHg) and higher (150 mmHg) pressure autoregulatory breakpoints, CBF falls and rises in direct proportion to corresponding changes in the CPP [9]. This theoretical nicety can be used practically to lower the ICP by pharmacologically elevating the MAP and thus the CPP. On account of pressure autoregulation, intracranial blood vessels would constrict and the CBV would be lowered as would the ICP. Care has to be taken, though, to determine the ‘high’ pressure autoregulatory breakpoint, as some patients, especially those with traumatic brain injuries, are likely to have disrupted homoeostasis. This breakpoint can be determined in the neurosurgical ICU in a patient with invasive arterial BP monitoring, a central venous pressure (CVP) line and an indwelling ICP pressure gauge. Inotropes can be used to increase the MAP. Initially, the ICP will remain steady or drop until the critical high pressure autoregulatory breakpoint is achieved, after which it will begin to rise quite dramatically. Most monitors will provide the MAP and ICP readings along with the CPP. The target CPP should be 5–10 mmHg less than this critical breakpoint.

Intracranial Hypertension (ICH)

Broadly speaking, ICH exists if the ICP is >20 mmHg. Elevations should be treated if this baseline is not reached within 5 min of any intervention as the ICP can increase transiently after suctioning, neurological examination using a painful stimulus and positioning. A myriad causes for ICH exist. Broadly, they may be classified as primary (intracranial), secondary (extracranial) and idiopathic (Table 6.1). ICH

Table 6.1 Causes of intracranial hypertension

A. Primary (intracranial)
i. Pathological IV space—tumour, haematoma, abscess, cyst
ii. Cerebral oedema—cytotoxic, vasogenic, interstitial, osmotic
iii. Hydrocephalus—communicating/obstructive
iv. Increase in cerebral blood volume—arteriovenous (AV) fistula/malformation
B. Secondary (extracranial)
i. Hypoventilation—hypoxia, hypercarbia
ii. Raised intrathoracic pressure—pneumothorax, haemothorax
iii. Obstruction of the internal jugular vein (IJV)—posture, tape compression, tumour
iv. Seizures
v. Hyperpyrexia
vi. Toxins—lead, tetracycline, rofecoxib
vii. Liver cell failure—Reye syndrome
C. Idiopathic (benign intracranial hypertension)

may be mild (ICP; 20–30 mmHg), moderate (30–40 mmHg) or severe (>40 mmHg). Sustained ICH of >40 mmHg is a life-threatening emergency [12].

After Lundberg's observations, lowering ICP, even at the cost of cerebral perfusion, became the guiding philosophy for most neurocritical specialists until the 1990s when centres began to realize that this strategy did not help reduce mortality. The focus then began to shift to the current guidelines, proposed by the Brain Trauma Foundation (BTF), of maintaining the ICP <20–25 mmHg and CPP 50–70 mmHg [13–15].

It should be made patently clear at the outset that reliable randomized controlled trials (Level of evidence 1/standards) for most of the therapeutic modalities available to neurosurgeons are singularly lacking. We only have guidelines (Level of evidence 2) and options (Level of evidence 3).

ICP Monitoring

ICP can be measured using transducers attached to probes located in the epidural, subdural, subarachnoid, intraparenchymal and intraventricular compartments. The gold standard is an intraventricular ICP monitor, otherwise known as an external ventricular drain (EVD). This dual-purpose device indicates the global ICP and helps CSF drainage when ICP is elevated [16]. It is the most accurate of all the above-mentioned devices, but may also be the most difficult to place in the chinked ventricles of a patient with a traumatic intracranial haematoma. Intraparenchymal devices have an advantage in this setting, but are better indicators of local pressure and should be placed ipsilateral to the pathology. The representative Camino system measures the amount of light reflected by ICP-induced movement of a small mirror at the parenchymal end of the catheter [17]. Our team commonly uses the Richmond subdural bolt—a fluid-coupled ICP monitoring device that is the oldest, simplest, least invasive and most economical way of monitoring the ICP. It consists of a hollow bolt screwed into a 0.25-inch trephine, which projects 1 mm below the inner table through the opened dura. Most surgeons opt to keep the arachnoid intact to prevent the brain from herniating into the dura or plugging of the device by debris [18].

Normal ICP Waveforms

The normal ICP waveform has a steady-state or baseline level on which pulsatile variations of the cardiac and respiratory cycles are imposed (Figs. 6.1 and 6.2). It is important to note the systolic, diastolic and mean ICP, as also its variability with the cardiac and respiratory pulses [9]. It is also vital to ensure that all transducers (except for the intraparenchymal catheters) are zeroed with the atmosphere at the level of the external auditory meatus. Our team has found this to be the most common cause of a false-positive raised ICP.

Fig. 6.1 Photograph of an ICP waveform. The scale has to be adjusted such that the normal waveform (in white) can be seen. This is synchronous with the cardiac rhythm and has a systolic, diastolic and mean value. In this case it is 7, 4 and 5 mmHg, respectively. The mean arterial pressure is 84 mmHg. Thus, the cerebral perfusion pressure is 79 mmHg



Fig. 6.2 Photograph of a patient undergoing ICP monitoring using a Richmond ICP bolt



Pathological ICP Waveforms

Lundberg, [8] in his seminal paper of 1960, described three kinds of pathological waveforms:

1. *Lundberg A waves*

These are plateau waves with the ICP increasing to 50 mmHg for 5–20 min. The MAP is increased concomitantly. It is unclear whether this is a cause or an effect.

2. *Lundberg B waves*

These are pressure waves with ICP pulses of amplitude 50 mmHg occurring every 30 s–2 min.

3. *Lundberg C waves*

These have a normal ICP waveform, amplitude of 20 mmHg and a frequency of 4–8/min [8].

Indications for ICP Monitoring

On the basis that ICP monitoring may help in the earlier detection of intracranial mass lesions, limit the indiscriminate use of therapies to control the ICP, reduce the ICP by CSF drainage, help in determining prognosis and possibly improve outcome, the BTF guidelines, issued in 2000 and 2007 (Level of evidence 2), are summarized in Table 6.2 [19]. They concluded that routine ICP monitoring is not indicated in patients with mild or moderate head injury except (and at the discretion of the treating physician) in patients with traumatic mass lesions [19].

In addition to the BTF recommendations, and on the basis of the experience of our own team, we would like to add two more indications that are not uncommon:

1. Mild-moderate head injuries with dominant temporal lobe contusions being managed conservatively
2. Trauma patients with an abnormal CT requiring sedatives or pharmacological paralysis for non-neurological procedures rendering them non-examinable for any period of time [20]

Contraindications to ICP monitoring are coagulopathies, immunosuppression, non-salvageable patients and compound depressed fractures where infection rates can approach 40% [21]. Complications include haematoma formation, malposition, malfunction, obstruction and a risk of colonization leading to serious CSF infection in 5–14% of cases [22]. Antibiotic-coated catheters may reduce the risk of infection from 9.4 to 1.3% [23].

Although intuitive logic dictates that ICP monitoring and CPP tailoring for individual patients would appear to decrease morbidity and mortality, Shafi et al. found that the BTF indications for ICP monitoring were being adhered to in only 43% of indicated cases [24]. Unfortunately, ICP monitoring in accordance with their criteria was associated with worsening of survival [24]. Only a well-designed, randomized prospective trial is likely to resolve this issue. Our team currently follows the BTF guidelines selectively.

Table 6.2 Indications for ICP monitoring (Brain Trauma Foundation) [19]

A. Severe head injury (post-resuscitation GCS score 3–8)
1. Abnormal CT head
2. Normal CT head and two or more of the following
(a) Age >40 years
(b) Uni-/bilateral motor posturing
(c) SBP <90 mmHg
B. Mild/moderate head injury (post-resuscitation GCS score 9–15) with
1. Intracranial traumatic mass lesions
2. At the discretion of the treating physician

GCS Glasgow Coma Scale

Clinical Features

Patients with raised ICP present with headache, nausea and projectile vomiting. Classically, an acute rise of ICP reflects in a III nerve palsy, especially with focal lesions, with or without papilloedema, whereas a chronically elevated ICP commonly results in VI nerve paresis (generally bilateral) and papilloedema. A deteriorating level of consciousness is an ominous sign that precedes the classical Cushing triad (hypertension, bradycardia and respiratory depression). This often corresponds to an ICP exceeding 40 mmHg. The corresponding drop in CPP and brain herniation caused by ICH may lead to irreversible brain infarction. A tense fontanelle in an infant is a useful sign of ICH.

Monitoring

Patients managed in a neurosurgical/neurological ICU require an acute level of care. Patients with borderline ICP are initially given the option of medical management; refractory ICP often needs surgical treatment. Thus, patients with a low Glasgow Coma Scale (GCS) score are often electively ventilated (<8, intubate) and monitored haemodynamically using hardware which includes, but is not limited to, CVP lines, arterial lines, Foley catheters, capnography, transcranial Doppler (TCD), bedside EEGs, jugular venous saturation (S_{jO_2}) probes and ICP measurement devices [20]. The parameters to be monitored are listed in Table 6.3. A few other monitoring aids are outlined below.

Laser Doppler Flowmetry (LDF)

LDF is used to monitor tissue perfusion with a parenchymal probe. The basis for this is a Doppler shift of reflected laser light caused by red blood cells moving

Table 6.3 Parameters monitored in patients with intracranial hypertension (ICH) [20]

1. Haemodynamic—respiratory
(a) Pulse
(b) Invasive arterial blood pressure
(c) Central venous pressure
(d) Arterial O_2 saturation
(e) End-tidal CO_2
(f) Temperature
2. Cerebral
(a) Intracranial pressure
(b) Brain tissue oxygenation
(c) Electroencephalography
3. Cerebrovascular
(a) Jugular venous oximetry
(b) Vasospasm

through microvessels. LDF has excellent dynamic resolution, but measurements are local, and the units are arbitrary and reported in mL/100 g/min. This information is extrapolated from an actual volume of only 1 mm³ that the probe is in contact with [25, 26].

Near-Infrared Spectroscopy (NIRS)

NIRS is a non-invasive tool used to measure brain function through the intact skull. It detects changes in blood haemoglobin concentrations associated with neural activity by using infrared light which penetrates a few centimetres through the tissue, as opposed to visible light which has a penetration of only a few millimetres. The amount of light recovered by NIRS depends on the amount of absorbance by haemoglobin, myoglobin and cytochrome aa3, as well as the degree of light scatter. Although values have always suffered from contamination by extracranial tissues, it has been shown that continuous online measurements of haemoglobin and cytochrome oxidase correlate well with simultaneous TCD studies and frontal cutaneous LDF [27].

Multi-Parametric Brain Tissue Monitoring

This technology helps in the acquisition, display, in-line analysis and recording of physiological parameters from multiple bedside sources using various software and hardware appliances capable of handling up to 32 parameters simultaneously. It assesses cerebrovascular autoregulation and reactivity using TCD, ICP, S_{BrO₂} and brain tissue oxygen (P_{BrO₂}) monitoring [28]. Another multi-parametric monitoring system—the ‘tissue spectroscope’—has also been used to assess brain oxygen balance. This comprises a surface fluorometer to evaluate mitochondrial function by estimating the NADH (reduced nicotinamide adenine dinucleotide) redox state, whereas LDF assesses the microcirculation. This combined optical probe can provide a significant correlation between CBF and brain tissue oxygenation [29].

Investigations

CT of the head and an MRI are the primary investigations that will determine the first step in the management of a patient with ICP. In an unconscious patient, a mass lesion will need to be evacuated urgently if associated with displacement of the ventricular system, a midline shift of >5 mm and effaced basal cisterns. In a conscious patient with traumatic brain injury without the above radiological findings, it would be inadvisable to monitor ICP initially, except in the singular condition of a patient having a contusion in his or her dominant frontal or temporal lobe. In such patients, the resulting aphasia will interfere with clinical assessment and

surgery will render permanent a possibly transient deficit. ICP monitoring obviates the need for clinical assessment and patients can be deeply sedated or even paralysed. In our unit, such patients have their serum electrolytes, blood glucose, arterial blood gases, chest X-rays and haemograms checked daily at the very least. Blood, urine and tracheal samples are obtained for culture twice a week or sooner if a clinical suspicion arises. The coagulation profile should be closely monitored as these patients can become surgical candidates within minutes. If unconscious patients, especially those with traumatic brain injuries, fail to improve, CT scans are repeated every 48 h for the first post-injury week to rule out a delayed intracranial haematoma.

Management

The protocol followed in our unit is described in Fig. 6.3. The first investigation ordered is a CT. A mass lesion with a significant midline shift is taken up for surgery. If radiological criteria are not fulfilled, patients can be given a trial of ICP monitoring and medical management. This generally lasts until the patient improves clinically, ICP is controlled or repeat imaging shows resolution of the mass lesion. ICP monitoring does not usually exceed 5 days as the monitor is removed to prevent colonization/infection.

General Medical Measures

Patient Positioning

Our group follows the recommendation that ICH patients be positioned with the head end of the bed elevated to 30°, as venous outflow and CSF displacement from the cranial cavity are maximized without compromising CPP [30]. It is also crucial to ensure that the tapes used to secure endotracheal or tracheostomy tubes do not compress the jugular veins. ICP and arterial BP transducers are zeroed with the atmosphere at the level of the foramen of Monro. To reduce subjective error, our group prefers using the external auditory meatus as the landmark.

Elective Ventilation

The BTF issued the following guidelines in 2007 [31].

- Level I: There are insufficient data to support a Level I recommendation.
- Level II: Prophylactic hyperventilation (PaCO_2 of ≤ 25 mmHg) is not recommended.
- Level III: Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP. Hyperventilation should be avoided during the first 24 h after injury when cerebral blood flow (CBF) is often critically reduced. If hyperventilation is used, S_{jO_2} or brain tissue oxygen tension P_{BrO_2} measurements are recommended to monitor oxygen delivery.

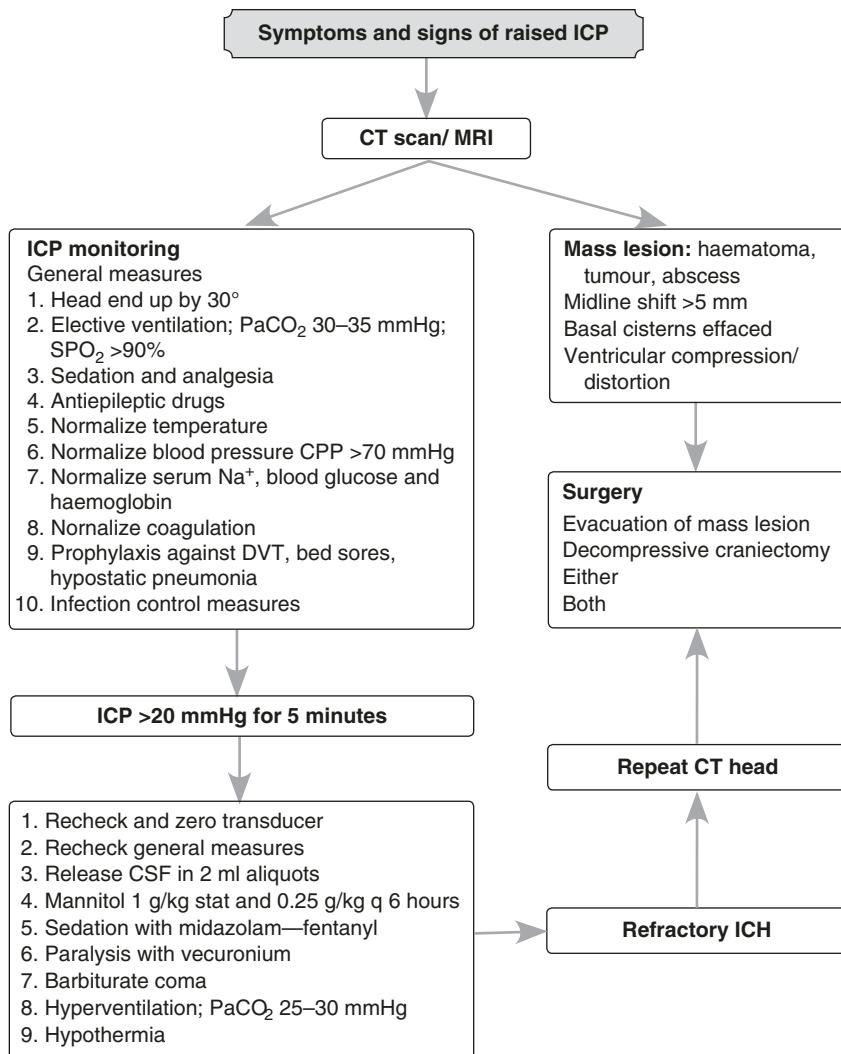


Fig. 6.3 Management algorithm for raised intracranial pressure. *CPP* cerebral perfusion pressure, *DVT* deep vein thrombosis, *ICP* intracranial pressure, *ICH* intracranial hypertension

We support the use of euventilation (PaCO_2 of 30–35 mmHg) as an initial response to an elevated ICP. Hyperventilation (PaCO_2 of 25–30 mmHg) is a second-line management option in patients with refractory ICP [32]. Hyperventilation has a danger of reducing the CBF as the cerebral vasculature constricts. Although the ICP may reduce transiently, new infarcts may develop with time, causing a delayed rebound rise [33].

Sedation and Analgesia

One of the pillars of conservative management of patients with traumatic brain injury used to be close clinical observation. This prevented the use of sedatives even in ventilated patients. This caveat can be overcome with ICP monitoring. A note of caution, however, is to not rely on a single parameter. Even though a sedated, ventilated patient may have a normal ICP, our team periodically corroborates this by tapering the sedation gradually and reassessing the patient's clinical status. As mentioned previously, we also repeat CT scans as a definitive objective countercheck to both clinical examination and ICP monitoring.

Drugs

(a) Morphine

- *PRN/loading dose:* 2–4 mg q 10 min till sedation/analgesia is achieved. There is no maximum dosage in acute care; only adverse drug effects limit dosage.
- *Continuous i.v. infusion:* 2–5 mg/h (100 mg morphine/50 mL 0.9% sodium chloride [34])

(b) Fentanyl

- This is used when the creatinine level is >200 µmol/L, morphine allergy is present or the patient is haemodynamically unstable.
- *PRN dose:* loading dose: 25–50 µg i.v. q 10 min until pain relief [34]
- *Continuous i.v. infusion:* 20 µg/h (1000 µg/50 mL 0.9% sodium chloride)
- Dosage should be individualized on the basis of patient response and tolerance.

(c) Midazolam

Midazolam should always be titrated slowly over at least 2 min. An initial bolus may be given at a dose of approximately 0.05 mg/kg.

• *Induction*

- *Healthy adults below the age of 60 years:* Titrate with 1–2.5 mg over a period of at least 2 min. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, use small increments and wait an additional 2 or more minutes after each increment. A total dose of >5 mg is not usually necessary.

- *Patients aged 60 years or older, and debilitated, or chronically ill patients:* Increments should be smaller and the rate of injection slower because of the risk of respiratory depression. No more than 1–1.5 mg should be given over a 2-min period. Wait an additional 2 min to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of not >1 mg over a period of 2 min, waiting an additional 2 min or more each time to evaluate the sedative effect. Total doses of >3.5 mg are usually not necessary.

• *Maintenance*

- Maintenance doses of midazolam may approach $0.04 \pm 0.03 \text{ mg/kg/h}$.

(d) Lorazepam

- *Loading dose:* 0.05 mg/kg
- *Maintenance dose:* 0.02 ± 0.01 mg/kg/h

(e) Propofol

- *Loading dose:* 0.25 mg/kg
- *Maintenance dose:* 2.0 ± 1.5 mg/kg/h

Lorazepam is a cost-effective choice for sedation, but over-sedation may be problematic. Midazolam is the most titratable drug that avoids over- or under-sedation. Trauma patients may respond inadequately to propofol even at higher doses (Level of evidence 1) [35].

The drugs of choice at our centre are a simultaneous fentanyl and midazolam infusion. Hypotension and delayed reversal may occur sometimes. The literature suggests that in the neurosurgical ICU, patients receiving infusions of remifentanil (0.1–0.2 µg/kg body weight/min) and propofol (0.5–3 mg/kg body weight/h) spent a shorter time on the ventilator and in the ICU compared with those infused with fentanyl (0.03–0.2 mg/h) and midazolam (2–12 mg/h) (Level of evidence 2) [36].

Antiepileptic Drugs (AEDs)

We prefer to administer AEDs prophylactically to all patients with recognizable intracranial mass lesions. A Cochrane analysis in 2006 found insufficient evidence to establish the net benefit of prophylactic AED treatment at any time after injury. Although prophylactic AEDs appeared to be effective in reducing early seizures, evidence was lacking to suggest that this reduced the occurrence of late seizures, death or neurological disability [37]. In the event of an acute seizure, the following drugs may be used for initial treatment:

- (a) *Lorazepam:* 0.1 mg/kg at 2 mg/min up to 5 mg
- (b) *Midazolam:* See above. Can load up to 0.2 mg/kg
- (c) *Diazepam:* 0.2 mg/kg at 5 mg/min up to 10 mg

Following initial treatment, any one of the following can be used for maintenance:

- (a) *Phenytoin:* 18–20 mg/kg loading dose at a rate not exceeding 50 mg/min in saline in a situation such as status epilepticus. A close watch on haemodynamic status and any allergic reaction is strongly warranted.
- (b) *Fosphenytoin:* 20 mg PE (phenytoin equivalents)/kg at a maximum rate of 150 mg/min.
- (c) Valproic acid/phenobarbitone may be used in a situation in which phenytoin or fosphenytoin is contraindicated, as both can be delivered rapidly intravenously.

The Brain Trauma Foundation (2007) guidelines offer Level 2 evidence that the prophylactic use of phenytoin or valproic acid is not recommended to prevent late

post-traumatic seizures (PTS). Anticonvulsants are indicated to decrease PTS. However, early PTS are not associated with worse outcomes [38].

For details on status epilepticus, please read Chap. 8 on ‘Generalized Convulsive Status Epilepticus’.

Normalize Temperature

Core temperature monitoring is essential for comatose patients as an increase in temperature can exacerbate brain hypoperfusion by increasing the oxygen demand [39]. Brain temperature may be measured directly by using intraparenchymal or epidural probes or indirectly by monitoring jugular bulb or temporalis muscle temperature [40]. Fever increases the metabolic rate by 10–13% per degree Celsius and may correlate with poor neurological outcomes [12]. Temperature may be reduced using antipyretics, cooling blankets, alternate cold and tepid water sponging, and ice-cold saline gastric lavage. The Brain Trauma Foundation (2007) guidelines do not offer Level 1 or Level 2 evidence to support prophylactic hypothermia [41].

Normalize BP

The goals of therapy involve maintaining an ICP of <20 mmHg and CPP of 50–70 mmHg. It is imperative to identify the best possible reason for the low BP and treat it accordingly. Colloid support as per the patient’s CVP using fresh whole blood, fresh frozen plasma (FFP) and high-molecular-weight dextrans (HMW-D) should be used to maintain a CVP of 10 cmH₂O where desired. Most cases of hypovolaemic shock encountered in the neurological/neurosurgical ICU relate to haemorrhagic and septic shock. Blood loss should ideally be replaced by blood. In the event of a shortage of blood products or extreme acuity, dextrans may be transfused to sustain circulation. Blood for cross-matching must be drawn before administration of HMW-D to avoid interfering with it. Coagulation disorders and allergic reactions too may be encountered in this setting. FFP transfusion is a valid substitute for volume replacement over HMW-D, especially when the patient’s haemoglobin exceeds 10 g%, but carries the risk of hepatitis and HIV infection. As several randomized controlled trials have shown no proof that resuscitation with colloids reduces the risk of death vis-à-vis crystalloids, in patients with trauma, burns or post-surgery, one should be cautious about their use. A Cochrane analysis in 2007 proposed that the continued use of colloids, which are more expensive than crystalloids, is unjustifiable outside the ambit of a randomized controlled trial [42]. If, after CVP correction, the CPP is still <70 mmHg, our group uses a combination of inotropes in the following order to increase the MAP:

- (a) Dopamine: 2–10 µg/kg/min infusion
- (b) Dobutamine: 2.5–15 µg/kg/min infusion
- (c) Noradrenaline: 0.1–1 mcg/kg/min
- (d) Adrenaline: 0.1–1 mcg/kg/min

Dopamine, with its easy availability, remains the drug of initial choice to treat hypotension in our ICU. However, at doses of <2 µg/kg/min, dopamine may be

associated with cerebral vasodilatation. At doses of $>10 \mu\text{g}/\text{kg}/\text{min}$, an unrestrained α -stimulation may result in cerebral vasoconstriction. It remains a first-line choice in treating septic shock. Its previously accepted virtue of renal protection is now acknowledged to be more mythical than factual. Norepinephrine is rapidly becoming the agent of choice in treating septic shock [43]. However, its effect on cerebral haemodynamics is far from clear. In healthy volunteers and anaesthetized patients, the effects of noradrenaline may vary. This may be explained, in part, by the effect of variations in PaCO_2 and by the anaesthetic agents themselves. Thus, despite an increase in MAP and therefore CPP, cerebral oxygenation may actually be reduced [44]. Dobutamine remains the drug of choice in handling cardiac circulatory failure. Adrenaline is useful in anaphylactic shock and as adjuvant therapy in septic shock.

Normalize Serum Na^+ , Blood Glucose and Haemoglobin

Hyponatraemia is a dreaded condition that must be detected early and corrected aggressively. Hyponatraemia can precipitate a worsening of the ICP secondary to osmotic cerebral oedema. Mannitol especially can be associated with the most bizarre electrolyte imbalances. Blood samples to check electrolytes must be sent daily and in all patients with neurological deterioration. We use 3% NaCl for correction in symptomatic patients with Na^+ values of 125–130 mEq/L and in all patients with serum Na^+ of $<125 \text{ mEq/L}$. The rate of correction should not exceed 12 mEq/24 h. A useful rule of thumb is to start a 3% normal saline infusion at about (weight [$\text{kg}/2$]) mL/h. The exact rate and duration of correction are factors of total body water and initial Na^+ [45].

Clinical and experimental data suggest that hyperglycaemia lowers the ischaemic neuronal threshold in the presence of neurological injury caused by stroke, trauma and subarachnoid haemorrhage [46]. Intravenous insulin may be more effective than glucose–potassium–insulin infusion. Both interventions carry a risk of hypoglycaemia. Stroke patients with a blood glucose level of $<180 \text{ mg/dL}$ may be managed conservatively (guidelines; Level of evidence 2) [47].

Anaemia may critically injure vulnerable neurons by aggravating damage secondary to hypoxia and hypotension. We use red blood cell transfusions to maximize the oxygen-carrying capacity of blood. Our trigger to replace blood is a haemoglobin concentration of 10 g/dL, whereas other centres use a cut-off of 7 g/dL [48]. The ideal target haemoglobin level, the optimal duration of maintaining this level and the ultimate effect of transfusion on neurological and functional outcome remain unclear [49].

Normalize Coagulation

It is our belief that a patient with ICH is a surgical candidate and conservative management is merely a temporizing measure that gives us time to convert a high surgical risk emergency procedure into a semi-elective one. Hence, all blood investigations and haemodynamic and respiratory abnormalities must be either normalized or mitigated to ensure the best possible outcome. Coagulation derangement is frequently observed in patients with haemophilia and traumatic brain injury (34% in one study), in those who have undergone heart valve replacements or in those who

are hypertensive and on aspirin therapy [50]. Platelet dysfunction in patients with renal failure on dialysis and platelet paucity in dengue haemorrhagic fever can make haemostasis after haematoma evacuation impossible. Prothrombin time, partial thromboplastin time, bleeding time and platelet counts are assayed in our unit before any surgical procedure. Attempts must be made to normalize these parameters with FFP, cryoprecipitate, clotting factors, vitamin K, platelet concentrates or single-donor platelet transfusions before surgery. In case of a life-threatening emergency, coagulation factor replacement is started perioperatively.

Prophylaxis Against Venous Thrombosis, Bed Sores and Hypostatic Pneumonia

Intensive physiotherapy of the chest and joints is vital to prevent systemic complications such as deep vein thrombosis (DVT), decubitus ulcers and pneumonia. Patients who are heavily sedated are at high risk. In a large meta-analysis, low-molecular-weight heparin (LMWH) and intermittent compression devices were effective in reducing the rate of DVT (Level of evidence 1). No statistical difference was seen in the rate of intracranial haemorrhage with the former [51]. The best LMWH regimen and timing remain unclear [52]. Our team starts LMWH subcutaneously once daily on postoperative day 1 in high-risk patients.

Infection Control Measures

The overall incidence of developing a culture-positive, hospital-acquired infection may be as high as 16.2% in a neurosurgical patient. The most common infections are generally pulmonary, followed by bloodstream, urinary, CSF and wound. The incidence of both neurosurgical and extra-neurosurgical site body fluid bacteriological culture positivity may decrease significantly after using a variable-duration, risk-stratified protocol of perioperative chemoprophylaxis (Level of evidence 2) [53].

Management of ICP of >20 mmHg

Recheck General Measures

ICP that remains above 20 mmHg for >5 min should raise an alarm. The first step is to recheck all the above-mentioned general measures. The transducer must be zeroed at the correct position and the ICP measured again after ruling out common causes, such as internal jugular vein compression, extreme cervical spine positions, pneumothorax and an air bubble within the pressure tubing of the ICP monitor.

Release CSF

The greatest advantage of an EVD is that it can be used to release CSF in tiny aliquots of 2–5 cc. This can greatly relieve ICH, especially in patients with reduced cerebral compliance. It is crucial to not over-drain the ventricles, as rapid changes in CSF dynamics and ICP can produce remote intracerebral haemorrhages [54, 55]. Moreover, the ventricles are in all likelihood chinked to begin with, and

large-volume CSF drainage may cause the ventricle to collapse onto the catheter and block its fenestrations. Subsequent ICP measurements and CSF drainage may then be compromised. This is the most effective physiological way of maintaining a normal ICP.

Hyperosmolar Therapy

Mannitol

The mainstay of medical therapy remains mannitol. Mannitol has rheological and osmotic effects. Immediately after infusion of mannitol, a fluid shift occurs from the interstitial compartment to the intravascular one causing an expansion of plasma volume and a reduction in haematocrit and blood viscosity. This improves cerebral perfusion and increases oxygen delivery to the brain. In patients with intact pressure autoregulation, the consequent decrease in the concentration of metabolites of anaerobic metabolism reverses cerebral vasodilatation, which reduces the CBV and thus the ICP. In patients with absent pressure autoregulation, the decrease in ICP is less pronounced [56]. Mannitol may also improve microcirculatory rheology [57]. It is also a free radical scavenger and may be directly neuroprotective. The osmotic effect of mannitol draws oedema fluid from the cerebral parenchyma within 15–30 min of infusion. Serum osmolarity should be kept at <320 mOsm/L to avoid hypovolaemia, hyperosmolarity and renal failure. In the presence of a disrupted blood–brain barrier, mannitol can accumulate within the cerebral parenchyma and draw fluid into it, thereby aggravating vasogenic oedema. For this reason, mannitol should be tapered before stopping therapy to prevent a rebound rise in ICP [12].

Both these mechanisms explain why intravenous bolus administration of mannitol lowers the ICP in 1–5 min with a peak effect at 20–60 min. The effect of mannitol on ICP lasts 1.5–6 h [58]. Mannitol is usually given as a bolus of 0.25–1.0 g/kg body weight. A higher dose is given when urgent reduction of the ICP is needed. We tend to withhold mannitol when the systolic BP is <100 mmHg. A higher dose of mannitol (1.4 g/kg body weight) is associated with significantly better results than lower doses or continuous infusion [57, 59]. Ordinarily, we do not administer mannitol for >3 days. Maintenance doses commonly used are between 0.25 and 0.5 g/kg q 6–8 h. Electrolyte and fluid depletion has to be carefully monitored and replaced during therapy. A Cochrane analysis performed in 2007 found only four trials providing Level of evidence 1 for using mannitol [60]. It was concluded that mannitol therapy in raised ICP may decrease mortality when compared with pentobarbital treatment, but may increase mortality when compared with hypertonic saline. It was also observed that ICP-directed treatment had a beneficial effect when compared with treatment directed by neurological signs and physiological indicators [60]. The routine use of mannitol in patients with acute ischaemic or haemorrhagic stroke cannot be supported by Level of evidence 1 [61]. The Brain Trauma Foundation (2007) guidelines do not offer Level 1 evidence in support of the use of hyperosmolar therapy. Level 2 evidence indicates that mannitol in doses of 0.25–1 g/kg body weight is effective in controlling raised intracranial pressure. Systolic blood pressure <90 mm Hg should be avoided [62].

Hypertonic Saline (HS)

HS (3–23.4%) reduces the ICP by causing an osmotic fluid shift from the cerebral parenchyma into the bloodstream. HS may be more effective at reducing the ICP than mannitol (Level of evidence 1) [63, 64]. HS is also the osmotic diuretic of choice in a hypovolaemic and hypotensive patient. Adverse effects include bleeding secondary to decreased platelet aggregation, prolonged coagulation time, hypokalaemia and hyperchloraemic acidosis [65]. A potential risk of precipitating central pontine myelinolysis in the presence of hyponatraemia should be remembered, and HS may be avoided in this situation where rapid changes of osmolality to lower the ICP are emergent [66]. There have been no trials that compare the effect of HS on mortality. Until such data are available, HS may be considered a therapeutic adjunct to the medical management of traumatic brain injury.

Deep Sedation/Paralysis

This has already been discussed in a previous section. Additional advantages of deep sedation (with midazolam) and neuromuscular blockade include the control of refractory seizures and hyperventilation induced by severe pneumonitis. We prefer deep sedation to paralysis as monitoring is easier. Tachycardia and hypotension will often be the end-points for dose titration.

Barbiturate Coma

The BTF guidelines issued in 2007 support the use of high-dose barbiturate therapy to control ICP refractory to all other conventional medical and surgical treatments. This is the only second-tier management strategy for which Level of evidence 2 is available. However, high doses of barbiturates are associated with serious complications and render patients neurologically un-examinable for several days [67, 68]. Commonly used drugs include the following:

1. Pentobarbital, which is given in a loading dose of 10 mg/kg body weight followed by 5 mg/kg body weight each hour for 3 h. The maintenance dose is 1–2 mg/kg/h, titrated to a serum level of 30–50 µg/mL or until the EEG ideally shows burst suppression.
2. Thiopental, which is given in a loading dose of 2 mg/kg body weight over 20 s. If the ICP is not lowered to <20 mmHg, a second bolus of 3 mg/kg body weight can be administered. The maintenance dose is a 3 mg/kg/h infusion. Thiopental may be more effective in controlling refractory ICH (Level of evidence 1) [69].

The mechanism of ICP reduction by barbiturates is unclear, but is probably due to a coupled reduction in CBF and the oxygen demand of the brain. The effect on the ICP is immediate. Complications include hypotension, hypokalaemia, respiratory depression, infections and hepatorenal dysfunction [70]. Ideally, S_{O_2} and continuous bedside EEG monitoring must accompany close systemic surveillance and screening for sepsis. Outcome analysis is lacking because of the high complication rate.

Hyperventilation

Decreasing the PCO₂ to <25 mmHg is detrimental to outcome. Use of hyperventilation in refractory cases when everything else fails should be supported by S_{JO2} and CBF monitoring to prevent ischaemia [32].

Hypothermia

Level of evidence 3 exists for the cautious use of hypothermia in adults. A meta-analysis of 13 well-designed randomized controlled trials holds that the greatest reductions in the risk of mortality and the most favourable neurological outcomes were observed when hypothermia was maintained for >48 h [71]. However, the potential benefits of hypothermia may be offset by a significant increase in the risk of pneumonia [71, 72]. In adults with traumatic brain injuries, hypothermia would be one of the last resorts for treating refractory ICH. In children with traumatic brain injury, the absence of phase III clinical trials has prevented the elaboration of definitive guidelines [73]. Controlled trials are lacking on which to base guidelines for acute ischaemic and haemorrhagic stroke. A few pilot studies have stressed the need for proactive anti-shivering therapy for successful cooling and slow controlled re-warming to avoid rebound brain oedema. Such patients have a high risk of developing infectious and cardiovascular complications [74].

Steroids

Steroids have not been included in this chapter in the management algorithm of ICP because they have a specific role in decreasing vasogenic cerebral oedema around primary and secondary brain tumours. Most patients will undergo surgery. The following drugs are used:

1. Dexamethasone: 4 mg i.v. q 6 h
2. Hydrocortisone: 100 mg i.v. q 6–8 h for sellar–suprasellar tumours

Steroids have no role in traumatic brain injury or spontaneous intracerebral haemorrhage [75–78].

Surgical Management

The quickest, most effective and definitive way of dealing with intracranial mass lesions with a midline shift and effaced basal cisterns is a directed neurosurgical procedure. Medical management is preferred in borderline cases with no clear-cut indications for surgery. In such patients with refractory ICP, a repeat CT is performed before shifting the patient to the operating theatre for a salvage decompressive craniectomy (DC). A posterior cerebral artery infarct with brain stem hypodensities is a contraindication to a major surgical procedure. Surgical options are discussed below.

External Ventricular Drain Placement

This has been dealt with in a previous section. This procedure can be performed within minutes under local anaesthesia at the patient's bedside. CSF release can prove to be life-saving.

Lumbar Drain Placement

Controlled lumbar drainage may be a safe, efficacious and minimally invasive method for treating refractory ICH even after the placement of ventriculostomies to release CSF. This could be another bedside alternative to defer DC [79].

Decompressive Craniectomy (DC)

DC involves the removal of the calvarial bone to reduce the ICP. This may be performed unilaterally, bilaterally, primarily (at the time of definitive surgery, e.g. removal of an acute subdural haematoma combined with bone flap storage in the subcutaneous tissue of the abdomen) or secondarily (removing the bone flap in the second stage after medical management has failed). This may be combined either with multiple durotomy (when the brain oedema is intense and produces a mass effect greater than the thickness of the subdural haematoma) or a formal duroplasty.

DC has been used as a last resort for refractory ICH caused by cerebral/cerebellar infarction, trauma, subarachnoid haemorrhage and spontaneous intracranial haemorrhage. DC has been shown to decrease the ICP and improve brain oxygenation and even functional outcome after head injury [80–82]. Yet, a Cochrane review found only a single randomized controlled trial that demonstrated a reduction in the risk of death and unfavourable outcome in children below the age of 18 years when medical treatment failed to control the ICP [83]. The results of non-randomized trials and controlled trials with historical controls suggest that DC may be a useful option in adults with refractory ICH [84]. The landmark multicentre decompressive craniectomy in diffuse traumatic brain injury (DECRA) trial concluded that in adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavourable outcomes [85]. Complications include hydrocephalus, venous infarction at the craniectomy site and subdural hygroma [81].

The Hemicraniectomy after Middle Cerebral Artery Infarction with Life-Threatening Edema Trial (HAMLET) was a multicentre trial which randomized patients to medical and surgical arms within 96 h of ictus [86]. The authors found that case fatality did reduce after surgery which was delayed for up to 96 h after stroke onset, but the functional outcome did not vary. They concluded that the decision to operate should be taken after close consultation with the relatives regarding survival and dependency. In a pooled analysis of patients enrolled in the DECIMAL (DEcompressive Craniectomy In MAlignant middle cerebral artery infarction) [87], DESTINY (DEcompressive Surgery for the Treatment of malignant INFarction of the middle cerebral arterY) [88] and HAMLET [86] trials, in those who were

randomized within 48 h of stroke onset, surgical decompression was found to reduce both poor outcome and case fatality [89]. A small study has also favoured the use of DC in venous infarction [90]. Primary or secondary DC in aneurysmal subarachnoid haemorrhage may also be helpful, regardless of the underlying aetiology and clinical grade of the patient on admission [91].

The role of DC in cerebellar infarction remains controversial and may be no better than simply an EVD placement [92, 93].

DC can be a life-saving salvage procedure for patients with refractory ICH. Questions regarding patient selection, timing of surgery, surgical technique, timing of cranioplasty and the management of complications will remain unanswered until the results of randomized controlled trials become available [94, 95].

Conclusion

ICH remains a devastating clinical challenge. No new therapeutic modalities for treating cerebral oedema and elevated ICP have evolved over the past 80 years [87]. Scanty Level of evidence 1 is available to scientifically validate the standard of care. Available guidelines are frequently contradicted by newer research. Raised ICP, not amenable to direct surgery, is best treated medically with proper patient positioning, elective ventilation, sedation and analgesia, ICP monitoring and CSF drainage. Mannitol and HS are osmotic diuretics that can effectively reduce the ICP. The use of barbiturate coma is the only second-tier management option that can be supported with Level of evidence 2. Hyperventilation and hypothermia may be attempted before the patient undergoes a DC. Treatment has to be individualized and ICP monitoring must be supplemented with clinico-radiological assessment. The aim of therapy is to maintain the ICP at <20 mmHg and CPP at 50–70 mmHg.

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Acute Visual Disturbances

7

Cédric Lamirel, Nancy J. Newman, and Valérie Bioussé

Introduction

The visual pathways traverse more than one-third of the brain, explaining why visual function is frequently affected by intracranial lesions and a wide range of neurological disorders. Visual disturbances such as monocular or binocular visual loss, visual hallucinations and diplopia may reveal a neurological disorder. Correct interpretation and evaluation of these visual changes may prevent further devastating neurological complications.

Examination of the Visual System

Monocular visual loss results from lesions anterior to the chiasm (i.e. the eye itself or the optic nerve), whereas binocular visual loss results either from bilateral anterior lesions or, more likely, from a chiasmal or retrochiasmal lesion. Monocular diplopia is essentially always ocular in origin, whereas binocular diplopia is caused by ocular misalignment resulting from lesions of the efferent system (i.e. supranuclear and internuclear pathways, ocular motor nuclei and cranial nerves, neuromuscular junction and extraocular muscles).

Many aspects of the examination of the visual system, such as pupillary examination, extraocular movements and fundoscopic examination, are part of the routine neurological examination. This chapter emphasizes those aspects of examination and visual changes that are particularly relevant to neurological emergencies.

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Visual Acuity

Visual acuity can easily be tested at the bedside or in the emergency department, given a cooperative patient. Each eye must be tested separately, and patients should wear their corrective lenses during the examination. Ideally, visual acuity is tested for distance using a Snellen chart. If it is tested with a near card and the patient is older than 50 years, reading glasses (or a +2.00 or +3.00 lens) must be used. It is also possible to estimate visual acuity by having the patient read your name tag or a magazine in the waiting room. If visual acuity can be improved when the patient looks through a pinhole (small holes made on a piece of cardboard), the problem is refractive or ocular, and not neurological in origin.

Colour Vision

Reduction in the saturation or brightness of colours may be an early sign of optic nerve disease. Colour vision can be tested with pseudoisochromatic colour plates; it is abnormal in both eyes of patients with congenital colour blindness (usually males) and in one eye of patients with unilateral optic nerve dysfunction. Colour vision can also be tested by presenting a bright red object to each eye and asking the patient to estimate the amount of 'desaturation' of the colour in one eye as compared to the other.

Visual Fields

Visual fields should be tested monocularly, since the overlap in binocular fields may mask monocular field defects. Central fixation must be maintained, while the patient is instructed to look at the examiner's opposite eye or nose and count fingers presented within the central 30°. Special attention should be directed to the horizontal and vertical axes of the visual field. The patient must perform the task equally well in all four quadrants. An abrupt change across the horizontal axis in one eye is most suggestive of optic nerve disease, whereas an abrupt change across the vertical meridian signals visual loss of intracranial origin. Finger movements may be used to screen the more peripheral visual field. Formal visual field testing provides a more standardized examination, reveals more subtle abnormalities and can quantify the defects in order to follow disease progression. Kinetic perimetry (Goldmann) has the advantage of charting the entire visual field, including the far temporal periphery. It can quickly establish the pattern of visual field loss in the ill, poorly attentive or elderly patient who requires continued encouragement to maintain fixation and respond appropriately. However, the quality of the field is examiner-dependent. Automated static perimetry is more sensitive, quantitative and reproducible, but it requires a good level of cooperation and attention from the patient [1].

Eye Movements

Ocular motility must be checked binocularly and then monocularly in the nine diagnostic positions of gaze. Each type of movement must be tested: saccade, smooth pursuit, oculovestibular reflexes and optokinetic nystagmus in the vertical and horizontal directions. Convergence should also be assessed. Ocular misalignment can be tested by the cover and cross-cover test, red glass test or Maddox rod. In the young child or uncooperative patient, looking at the corneal light reflexes is a reliable way to detect ocular misalignments. Head position is also helpful when assessing ocular movements; the head is often moved in the opposite direction of the misalignment in order to suppress diplopia, and the head of a patient with a IV nerve palsy is usually tilted to the opposite side. Nystagmus must be assessed in primary gaze and eccentric gaze and at near vision. The position of the lids (ptosis or retraction), protrusion of the eyes (proptosis) and pupillary reactions are essential in understanding the mechanism of ocular misalignment.

Pupils

When assessing the possible causes of visual disturbances, the size and reactivity of the pupils should be carefully examined in the light and in the dark and with accommodation (at near). The presence of a relative afferent pupillary defect (RAPD) is characteristic of a unilateral or asymmetrical optic neuropathy in the setting of a retina that appears normal. Ocular diseases, such as corneal abnormalities, cataracts and most retinal disorders, do not cause a RAPD. The exceptions include severe retinal diseases, such as retinal vascular occlusions and large retinal detachments, which are easily seen on fundoscopic examination [2]. Anisocoria may be associated with a III nerve palsy or a Horner's syndrome, both classic signs of neurological emergencies.

Ocular and Fundus Examination

The ocular examination itself is usually the domain of the ophthalmologist, but careful penlight examination at the bedside may reveal abnormalities of the cornea or lens that could be the cause of decreased vision or that could obstruct an adequate view of the fundus [3]. Redness of the conjunctiva usually indicates a problem with the anterior segment of the eye. Abnormalities of the ocular media sufficient to cause severe visual loss usually result in a poor view of the ocular fundus: 'If you cannot see in, the patient cannot see out'. To view the ocular fundus to the best advantage, the pupils should be dilated. Short-acting agents that block parasympathetic transmission (tropicamide) or enhance sympathetic activity (phenylephrine) are typically used in combination. Dilatation occurs within 30 min and usually resolves within 6 h. Visible causes of central visual loss can be identified in either

the optic disc or the macula. Although more peripheral retinal findings may provide important diagnostic clues, it is primarily a disease of the optic nerve or the most central retina that results in loss of central visual function. Pertinent changes include disc oedema or disc atrophy; whitening of the inner retinal layers secondary to infarction, as in central and branch retinal artery occlusions; haemorrhages and venous dilatation in central retinal vein occlusion; detachment of the retina or accumulation of subretinal fluid, as in central serous retinopathy; and degeneration of the retina, as in age-related macular degeneration [1]. The source of transient visual loss may be suggested by abnormalities of the retinal vasculature, such as intraluminal particulate matter which may be calcific emboli from the heart or refractile cholesterol emboli from the carotid arteries or aortic arch. Infections such as syphilis or systemic inflammatory disorders such as sarcoidosis may cause vasculitis with arterial or venous sheathing and exudate deposits.

Vision Loss

In most cases, vision loss results from ocular disorders, and a detailed ocular examination must be performed by an ophthalmologist before the patient is evaluated for neurological disorders. However, specific causes of visual loss, such as optic neuropathies and bitemporal and homonymous hemianopia, result from neurological disorders. Monocular visual loss results from lesions of the eye or the optic nerve, whereas binocular visual loss most often results from lesions of the chiasm or retrochiasmal visual pathways. Whether transient or permanent, acute visual loss is a common complaint in the emergency room and may constitute a neurological emergency.

Acute Monocular Vision Loss

Ocular Causes of Acute Monocular Vision Loss

Acute monocular vision loss with eye pain, photophobia, tearing and redness of the eye suggests an ophthalmological disorder of the anterior part of the eye. Trauma, corneal infections, anterior uveitis and acute angle-closure glaucoma are classic causes of acute visual loss with pain, which should always prompt immediate examination by an ophthalmologist [4–9].

Intravitreal haemorrhage causes acute visual loss without pain. The anterior segment of the eye looks normal, there is no RAPD and it is impossible to view the fundus with the ophthalmoscope, which shows only an altered red reflex. Vitreous haemorrhage is common in persons with diabetes, but it may also occur in patients with acute intracranial hypertension, particularly those with subarachnoid haemorrhage (Terson syndrome) [10].

Retinal diseases, such as central retinal vein occlusion (Fig. 7.1), central retinal artery occlusion (Fig. 7.2) and retinal detachment, can produce acute painless monocular visual loss. In the elderly patient with age-related macular degeneration, metamorphopsia and acute monocular visual loss are often due to bleeding of a

Fig. 7.1 Central retinal vein occlusion with numerous retinal haemorrhages, dilatation of the veins and disc oedema

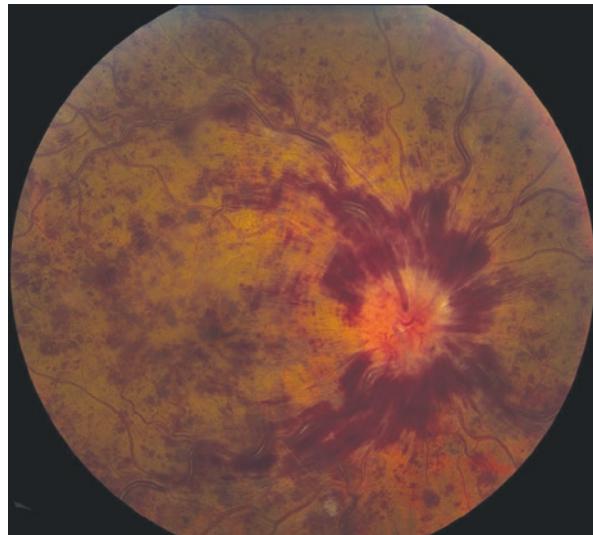


Fig. 7.2 Central retinal artery occlusion with a cherry-red spot. The ischaemic retina is oedematous and appears whitish and the arteries are attenuated



neovascular membrane [11]. Examination of the fundus by an ophthalmologist provides an immediate diagnosis [1, 12].

Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) produces acute, painless, severe and permanent monocular visual loss. Because the inner retinal layers, including the ganglion cells and their nerve fibres, are ischaemic, there is a dense RAPD. Fundoscopic examination shows attenuation of the retinal arteries, sometimes occluded by emboli, and whitening of the ischaemic inner retina, with sparing of the outer

retina in the foveal region supplied by the intact choroidal circulation, creating the classic ‘cherry-red spot’ (Fig. 7.2) [1, 12]. Carotid or cardiac sources of embolic disease should be investigated, as in the protocols for investigating ischaemic stroke [13]. In patients older than 50 years, giant cell arteritis must be ruled out by obtaining the complete blood count (CBC) with platelets, ascertaining the level of C-reactive protein (CRP) and measuring the erythrocyte sedimentation rate (ESR) emergently [14, 15].

Optic Neuropathies

Optic neuropathies present with decreased visual acuity, altered colour vision and abnormal visual fields. There is always a RAPD when the optic neuropathy is unilateral or asymmetrical. The optic nerve may be normal in the acute stage (when the posterior part of the optic nerve is involved) or may be swollen (when the optic nerve head is involved). In all cases, the optic nerve becomes pale 4–6 weeks later. There are numerous mechanisms of optic neuropathies (Table 7.1), and the diagnosis is most often suspected on the basis of the history and clinical examination. Specific imaging of the optic nerve is often helpful, particularly to demonstrate optic nerve inflammation, infiltration or compression. A dedicated MRI of the orbits without and with contrast and with fat suppression is the most sensitive test; a CT of the orbits without and with contrast, thin cuts and coronal reconstructions can also be helpful.

Table 7.1 Differential diagnosis of optic neuropathy

Inflammatory
• Idiopathic inflammatory optic neuritis
– Isolated
– Associated with multiple sclerosis
– Acute disseminated encephalomyelitis (ADEM)
– Neuromyelitis optica (NMO: Devic disease)
• Systemic inflammatory and autoimmune diseases
• Infectious diseases
Vascular: Ischaemic optic neuropathy
• Anterior/posterior
• Arteritic/non-arteritic
Compressive/ infiltrative
• Neoplastic
• Non-neoplastic
Toxic/nutritional
Hereditary
Traumatic
Raised intracranial pressure (papilloedema)
Glaucoma
Anomalous optic nerve
• Congenitally anomalous
• Drusen
• Myelinated nerve fibres

Ischaemic Optic Neuropathy

Ischaemic optic neuropathies are classified into anterior ischaemic optic neuropathy (AION), in which the optic nerve head is ischaemic, and posterior ischaemic optic neuropathy (PION), in which the posterior part of the optic nerve is ischaemic [16]. AION is much more common than PION, the latter remaining a diagnosis of exclusion. Ischaemic optic neuropathies are also classified as ‘non-arteritic’ and ‘arteritic’ (most often associated with giant cell arteritis).

In AION, the optic disc is swollen acutely, whereas the optic nerve appears normal in the acute stage in PION (Figs. 7.3 and 7.4). In both cases, there is painless

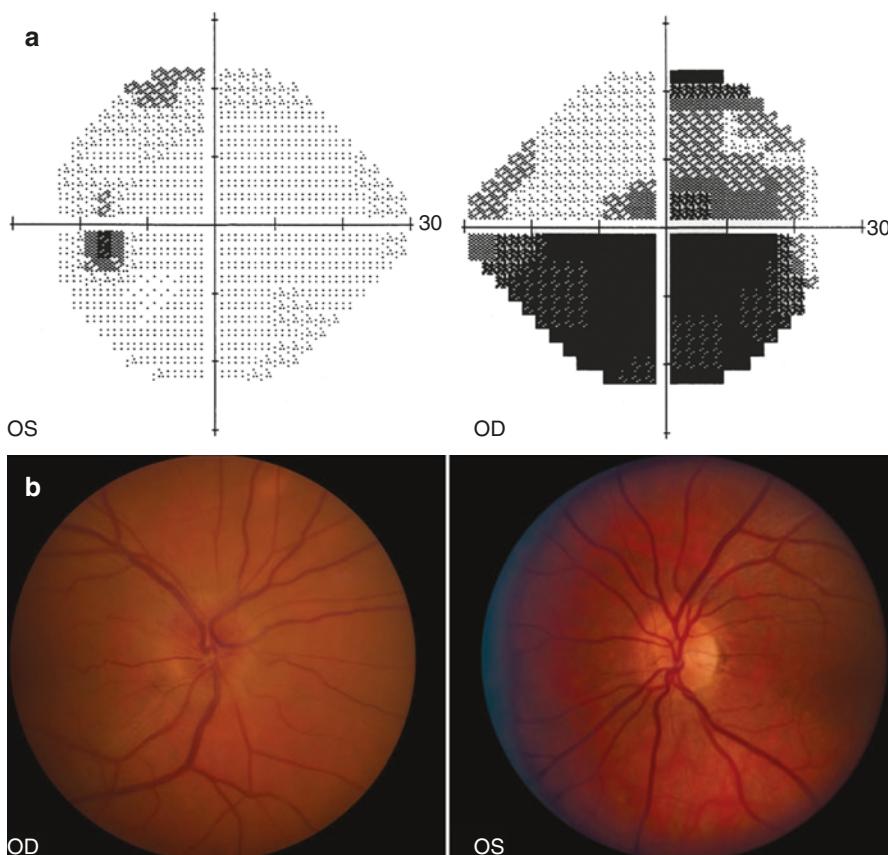


Fig. 7.3 Non-arteritic anterior ischaemic optic neuropathy in the right eye. (a) Automatic Humphrey visual fields on the 24-2 SITA standard protocol (the right eye visual field is shown on the right and the left eye visual field on the left). There is diffuse depression with an inferior altitudinal defect and a central scotoma in the right eye. The left visual field is full. (b) Fundus photography of both eyes (the right eye fundus is shown on the left and the left eye fundus on the right). In the right eye, there is mild optic disc oedema. In the left eye, the optic nerve is crowded, with a very small cup-to-disc ratio, consistent with a so-called ‘disc at risk’ for non-arteritic anterior ischaemic optic neuropathy

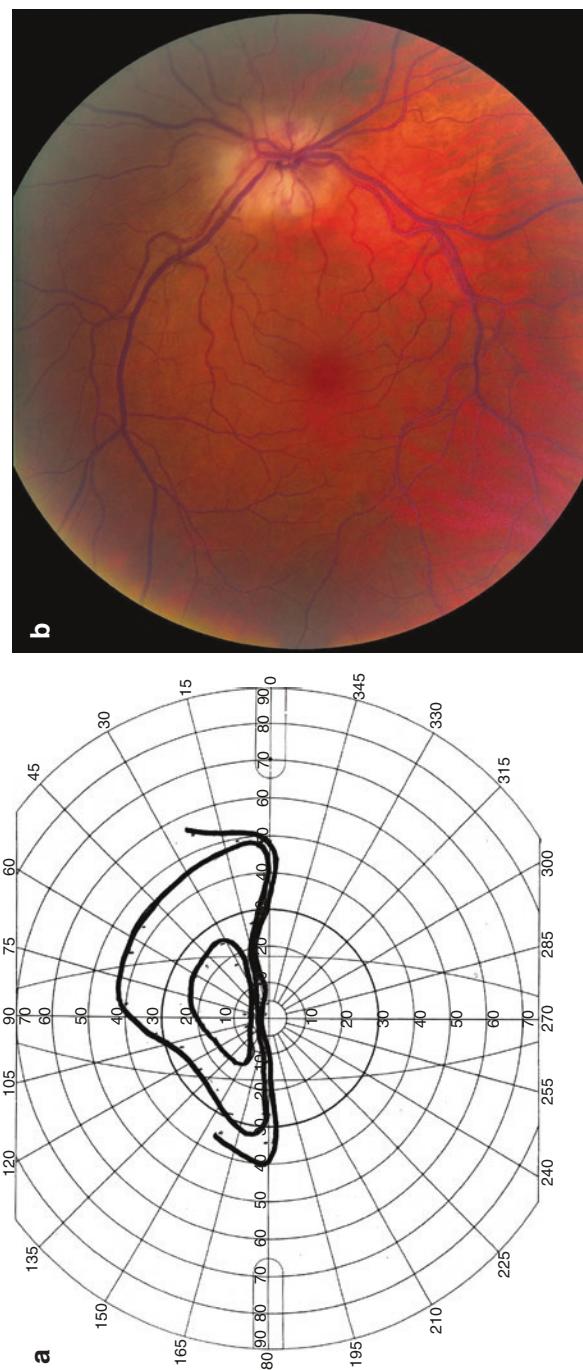


Fig. 7.4 Arteritic anterior ischaemic neuropathy in the right eye of a patient with giant cell arteritis. (a) Altitudinal inferior visual field defect on a Goldman visual field. (b) Fundus photography of the right eye showing palid disc oedema suggestive of an arteritic form of ischaemic neuropathy

acute or subacute visual loss, with visual field defects and a RAPD when the optic neuropathy is unilateral or asymmetrical; the optic nerve becomes pale 4–6 weeks later.

The most common form of ischaemic optic neuropathy is non-arteritic AION, which affects between 2 and 10 individuals per 100,000 (Fig. 7.3). The main risk factor is a small, crowded optic disc with no cupping (so-called disc at risk), but other anomalies, such as optic nerve head drusen and papilloedema, can underlie non-arteritic AION [17, 18]. Two-thirds of patients with non-arteritic AION also have at least one cardiovascular risk factor, but there is no increased risk of cerebrovascular disease in patients with non-arteritic AION [19, 20]. Because AION is a disease involving very small branches of the posterior ciliary arteries, the pathophysiology involves local atheromatous disease in addition to a predisposed anomalous crowded optic nerve. AION is not an embolic disease, and these patients should not be evaluated similar to patients with retinal or cerebral ischaemia. There is no proven treatment for ischaemic optic neuropathies, and the only emergency in evaluating a patient with AION or PION is to rule out giant cell arteritis [17]. Indeed, giant cell arteritis should always be considered in all patients with AION or PION, and blood tests looking for a biological inflammatory syndrome need to be obtained emergently in patients older than 50 years (Fig. 7.4). Steroids are initiated only in patients in whom there is high clinical suspicion, and a temporal artery biopsy is subsequently obtained when the diagnosis of giant cell arteritis is suspected [21, 22].

Optic Neuritis

Inflammation of the optic nerve is common and may occur in isolation, with multiple sclerosis, or in association with numerous infectious and noninfectious inflammatory disorders. Isolated optic neuritis is often the first manifestation of multiple sclerosis and is one of the classic clinically isolated syndromes.

Patients with optic neuritis present with acute or subacute painful monocular visual loss. Central vision typically deteriorates over days, and pain on eye movement is a frequent early complaint. On examination, there is decreased visual acuity, decreased colour vision and visual field loss centrally [23]. A RAPD is identified if the optic neuritis is unilateral or asymmetrical. In isolated optic neuritis associated with demyelinating disease, optic disc oedema is found in one-third of patients, whereas two-thirds have a normal optic nerve acutely. Persons with a normal optic nerve acutely are called patients of ‘retrobulbar’ or ‘posterior’ optic neuritis, whereas those with optic nerve oedema are called patients of ‘anterior’ optic neuritis (also called ‘papillitis’) (Fig. 7.5). In all patients, optic nerve head pallor develops 4–6 weeks later [24].

Evaluation of the patient with optic neuritis varies, depending on the clinical presentation and the suspected diagnosis. A brain MRI is usually obtained in patients with isolated optic neuritis to look for abnormalities suggestive of demyelinating disease. Various blood tests and serologies are also often obtained to investigate for alternate infectious and inflammatory disorders [25, 26]. In addition, a lumbar

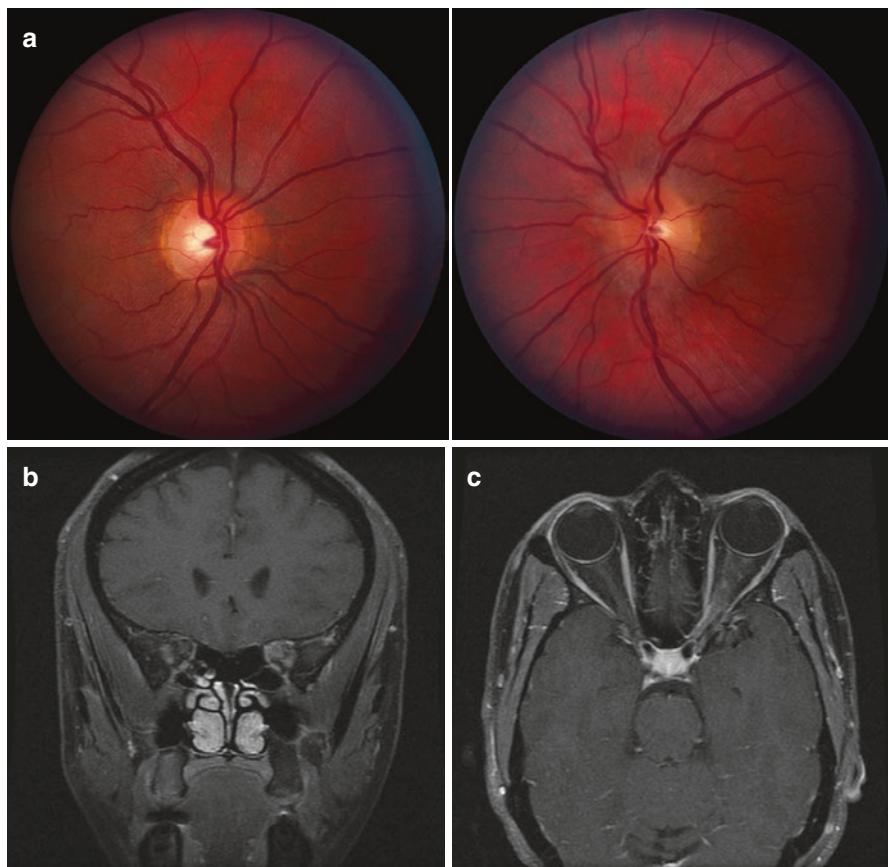


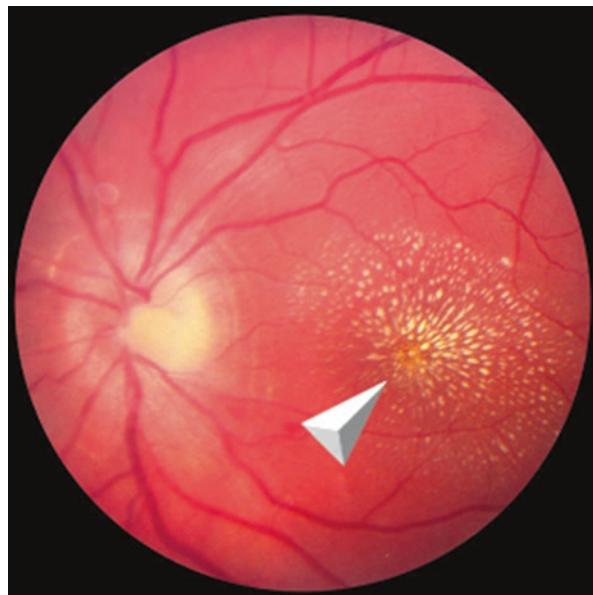
Fig. 7.5 Isolated left optic neuritis. (a) Fundus photo of both eyes showing very subtle disc oedema in the left eye (the right eye fundus is shown on the left and the left eye fundus on the right). Coronal (b) and axial (c) T₁-weighted MRI of the orbits with contrast and fat suppression demonstrating enhancement of the left optic nerve (arrowhead)

puncture may be useful in this setting. However, in most patients, optic neuritis remains idiopathic or is associated with multiple sclerosis.

In patients with typical isolated optic neuritis, the risk of multiple sclerosis is best predicted with the results of the brain MRI: patients with a normal brain MRI have a risk of multiple sclerosis estimated at 25% at 15 years, whereas those with at least one typical demyelinating lesion on the MRI have a risk close to 70% at 15 years [27]. The visual prognosis of isolated optic neuritis is usually good, and treatment for multiple sclerosis may be recommended for selected high-risk patients on the basis of clinical and radiological criteria.

Neuroretinitis characterizes a small subgroup of patients with an anterior optic neuritis associated with retinal exudates (Fig. 7.6). In most cases, neuroretinitis is

Fig. 7.6 Left neuroretinitis secondary to cat-scratch disease. There is disc oedema with macular exudates forming a 'star' consistent with a 'macular star'



due to an infection such as cat-scratch disease or syphilis or to a noninfectious inflammatory disorder such as sarcoidosis. Neuroretinitis is not associated with a subsequent risk of multiple sclerosis [28].

Traumatic Optic Neuropathy

Visual loss after head trauma is not uncommon and may be due to direct or indirect traumatic optic neuropathy [4]. Because these patients often have associated brain and systemic injuries, they are usually not managed primarily by neurologists. However, neurologists are usually involved at some point in the care of these patients, and they should be aware of the possibility of severe unilateral or bilateral central visual loss after head trauma. The method of treatment of these patients is controversial, but it now appears that high-dose steroids may cause more harm than good, especially if administered more than 8 h after the injury [4].

Compressive Optic Neuropathy

Compression of the optic nerve produces progressive unilateral optic neuropathy, with monocular, painless, progressive visual loss in most cases. These patients are usually not seen emergently. The classic causes include unrecognized pituitary tumours, meningiomas and ophthalmic artery aneurysms. Occasionally, the intra-cranial optic nerve may be rapidly compressed by ophthalmic or internal carotid artery aneurysms or by neoplasms (usually metastases) or by infectious lesions (mucormycosis in patients with diabetes) involving the orbital apex. These patients can present with very rapidly progressive optic neuropathies, and emergent evaluation and treatment are necessary.

Binocular Vision Loss

Persistent binocular visual loss may result from simultaneous damage to both optic nerves, to the chiasm or to the retrochiasmal visual pathways. If visual field testing reveals visual loss that respects the vertical meridian, the lesion must be at the level of the chiasm or more posterior. Unilateral retrochiasmal lesions will not change a patient's visual acuity. If visual acuity is affected because of bilateral retrochiasmal lesions, the loss of visual acuity must be identical in the two eyes. If visual acuity is asymmetrical, there must be some abnormality anterior to the chiasm ipsilateral to the eye with the worse vision.

Acute Bilateral Optic Neuropathies

Few causes of optic neuropathies classically involve both optic nerves simultaneously. These patients have bilateral visual loss and often present to the emergency department. Because both optic nerves are affected, there may not be a RAPD on examination, but the pupils are sluggish in response to light. However, when the optic nerves are normal acutely (such as from bilateral posterior optic neuropathies), the diagnosis may be difficult.

Bilateral simultaneous ischaemic optic neuropathies are highly suggestive of giant cell arteritis. This diagnosis is suspected in patients above 50 years of age and when there is optic nerve head oedema (AION). However, bilateral PION presents with a fundus that appears normal acutely and should be considered in this setting [16].

Raised intracranial pressure produces bilateral papilloedema, which may cause bilateral visual loss and secondary optic atrophy if not appropriately treated [29]. All causes of raised intracranial pressure can produce visual loss from papilloedema. Usually, central visual acuity is spared, and the major morbidity is constriction of the peripheral visual fields, classically over weeks or months. However, a fulminant form of idiopathic intracranial hypertension can cause rapidly progressive vision loss (Fig. 7.7) [30, 31]. The fundus shows bilateral severe papilloedema, which requires emergent treatment of raised intracranial pressure to prevent further visual loss.

Malignant systemic hypertension can also result in bilateral optic nerve head oedema and visual loss (Fig. 7.8). Hypertensive retinopathy can mimic papilloedema from raised intracranial pressure, and the blood pressure must be checked in all patients with bilateral disc oedema.

Bilateral optic neuritis, with or without disc oedema, should suggest an infectious or inflammatory disorder and should prompt a more extensive evaluation than isolated unilateral optic neuritis. Disorders such as acute disseminated encephalomyelitis (ADEM), infectious meningeal processes, sarcoidosis and neuromyelitis optica classically cause bilateral optic neuritis.

Patients with Leber hereditary optic neuropathy may present with acute or subacute painless bilateral optic neuropathies, mimicking bilateral optic neuritis but without pain [32]. The disease is maternally inherited and has been linked to point mutations in the mitochondrial DNA, which is routinely tested on a blood sample [33].

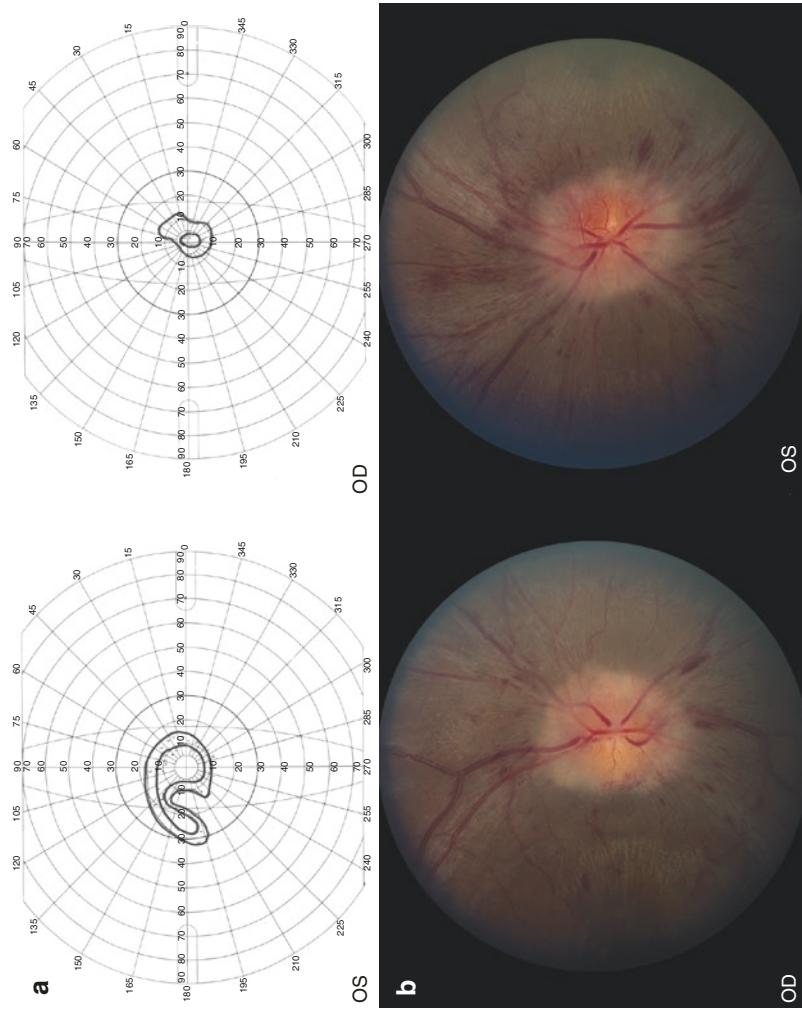


Fig. 7.7 Bilateral papilloedema secondary to fulminant idiopathic intracranial hypertension. **(a)** Goldman visual fields showing severe constriction in both eyes. **(b)** Fundus photos showing severe bilateral papilloedema with elevation of the optic nerves, blurry disc margins and papillary haemorrhages



Fig. 7.8 Hypertensive retinopathy with bilateral optic nerve oedema. Blood pressure was 210/140 mmHg. There are retinal exudates (arrowheads) and haemorrhages (arrow)

Acute Bilateral Vision Loss from Chiasmal Lesions

The most common cause of chiasmal syndrome is compression of the chiasm and intracranial optic nerves by a mass, such as pituitary tumours, sphenoid wing meningiomas and craniopharyngiomas. These patients usually present with progressive bilateral optic neuropathies and are not seen emergently. However, pituitary apoplexy, often associated with headaches, is a classic cause of acute chiasmal syndrome (Fig. 7.9). Visual loss may be isolated or associated with diplopia and altered mental status. The finding of a bitemporal visual field defect—the hallmark of a chiasmal syndrome—requires immediate brain imaging in patients with acute visual loss.

Acute Bilateral Vision Loss from Retrochiasmal Lesions

An acute homonymous visual field defect results from injury to the contralateral optic tract, lateral geniculate body, visual radiations or occipital cortex [1, 34, 35]. Visual acuity should be normal in each eye, unless there is superimposed damage to the anterior visual pathways or there is bilateral homonymous hemianopia (from bilateral occipital lobe lesions). A complete homonymous hemianopia has no further localizing value. Incomplete homonymous hemianopias may be congruous (when the two abnormal fields are similar) or incongruous (when the two abnormal hemifields are different). Determination of whether a homonymous hemianopia is congruous or not is helpful in localizing the lesion along the optic radiations towards the occipital lobe: ‘the more congruous a partial homonymous defect, the more posterior the lesion’ (Fig. 7.10). Associated symptoms and signs are also helpful in localizing the lesion along the visual pathways. The most common aetiology of isolated homonymous hemianopias is stroke, often an infarction in the territory of the contralateral posterior cerebral artery (Fig. 7.11) [36, 37]. Acute bilateral homonymous hemianopia with bilateral visual acuity loss can result from bilateral posterior cerebral artery infarctions, superior sagittal sinus thrombosis or posterior

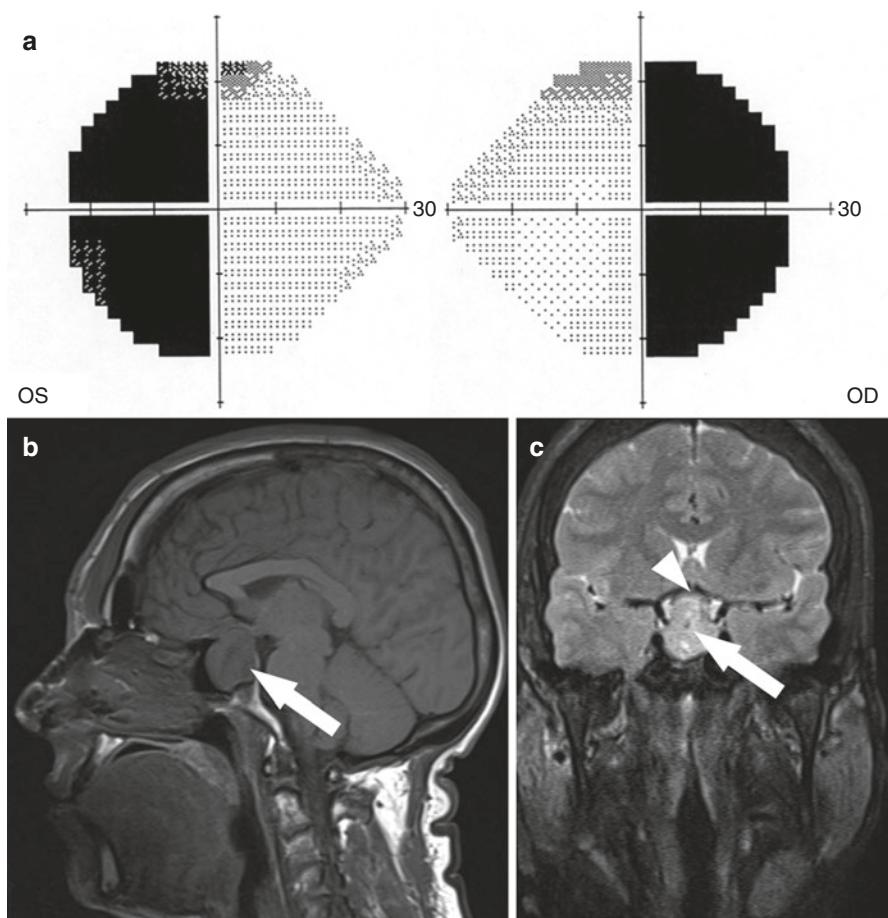


Fig. 7.9 Pituitary apoplexy with acute bilateral visual field loss and diplopia. (a) Humphrey visual fields showing a bitemporal hemianopia. (b) Sagittal T₁-weighted MRI of the brain without contrast showing enlargement of the pituitary gland compressing the chiasm (arrow). (c) Coronal T₂-weighted MRI demonstrating the suprasellar extension of the pituitary mass (arrow) and causing compression of the optic chiasm (arrowhead)

reversible encephalopathy syndrome secondary to malignant hypertension, eclampsia and uraemic encephalopathy and treatment with tacrolimus or cyclosporine [38]. An MRI of the brain following the stroke protocol is essential for the evaluation of patients with acute homonymous visual field defects.

Transient Visual Loss

The most important question to answer when evaluating a patient with transient vision loss is whether the vision loss is monocular or binocular. Monocular visual

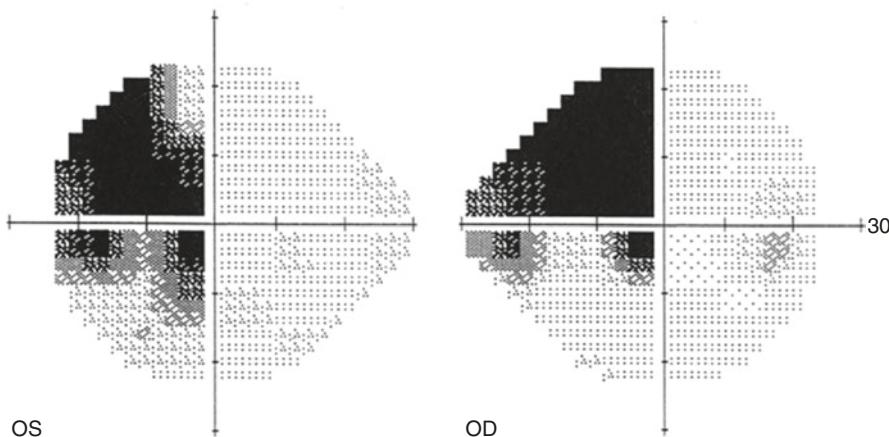


Fig. 7.10 Humphrey visual fields showing an incongruous left superior homonymous hemianopia

loss indicates a lesion of the eye or optic nerve, whereas binocular visual loss most often indicates lesions of the chiasm or retrochiasmal visual pathways. This distinction may be difficult because most patients do not think of closing either eye when visual loss is transient. Difficulty in reading and respect of the vertical meridian are two characteristics highly suggestive of binocular visual loss (and, therefore, of localization to the intracranial visual pathways). It is important to distinguish whether transient visual loss is monocular or binocular since the causes and workup differ accordingly.

Monocular Transient Visual Loss

Neurologists are often called to evaluate patients with transient monocular visual loss (TMVL). TMVL may result from a retinal transient ischaemic attack (TIA) in the carotid circulation and should be managed emergently, similar to hemispheric TIAs, in order to reduce the risk of permanent visual loss, stroke or cardiovascular death [39, 40]. However, because numerous ocular conditions can also produce TMVL and because fundoscopic examination may show retinal ischaemia and emboli acutely after an episode of TMVL, the patient should be evaluated emergently by an ophthalmologist before obtaining a further workup (Fig. 7.12).

Ocular Causes of Monocular Transient Visual Loss

Most ocular disorders can produce fluctuations in vision and may be described as ‘TMVL’ by patients. Dry eyes and other corneal surface disorders cause alterations in the tear film, often worsened by reading (during which blinking is reduced), and produce blurry vision that improves when the patient blinks a few times or rubs the eye. Acute increase in intraocular pressure can produce episodes of TMVL, with the patient often seeing halos around lights and suffering eye pain. Such episodes are

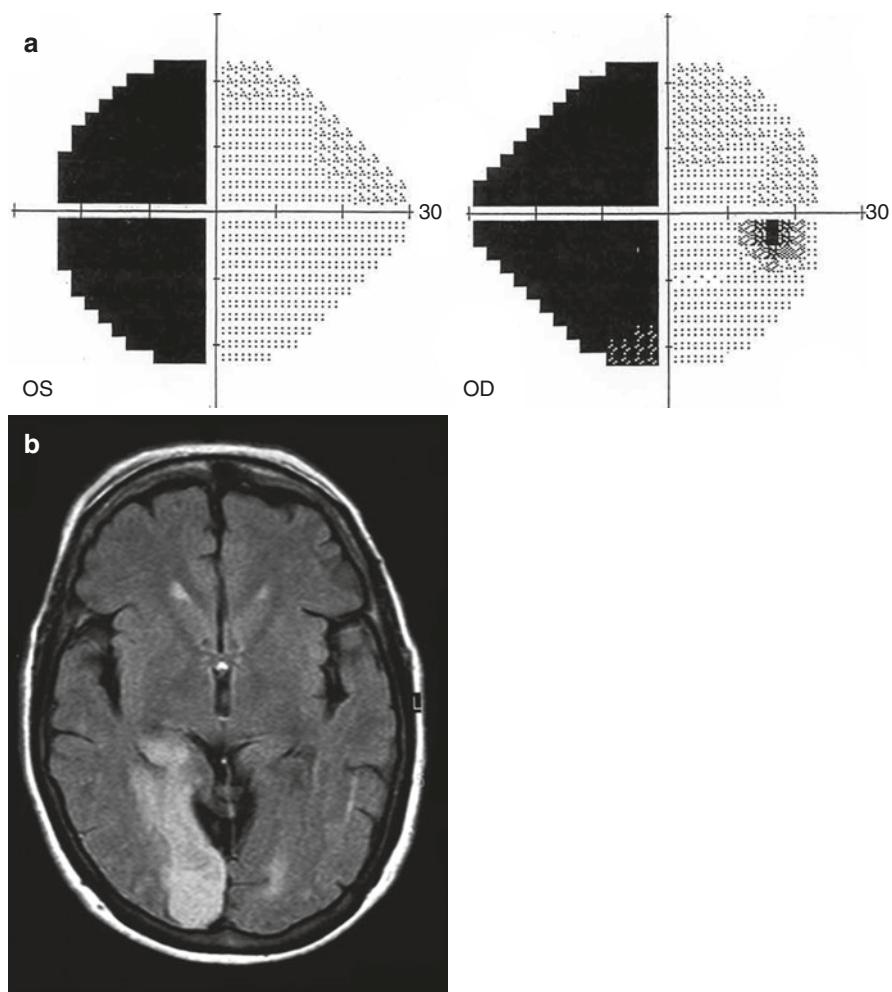


Fig. 7.11 (a) Humphrey visual fields showing a complete left homonymous hemianopia. (b) FLAIR axial MRI of the brain showed a right occipital infarction in the territory of the right posterior cerebral artery

suggestive of spontaneously resolving angle-closure glaucoma, precipitated by dim light in hyperopic patients and pigmentary dispersion after exercise in young myopic patients. In patients with diabetes mellitus, acute hyperglycaemia can cause TMVL lasting hours to days. Anomalous optic discs, such as papilloedema, drusen and tilted optic discs, can produce recurrent episodes of TMVL that last a few seconds (transient visual obscurations) and are precipitated by changes in posture (Fig. 7.7). Orbital tumours may present as episodes of monocular TMVL precipitated by eye movements.

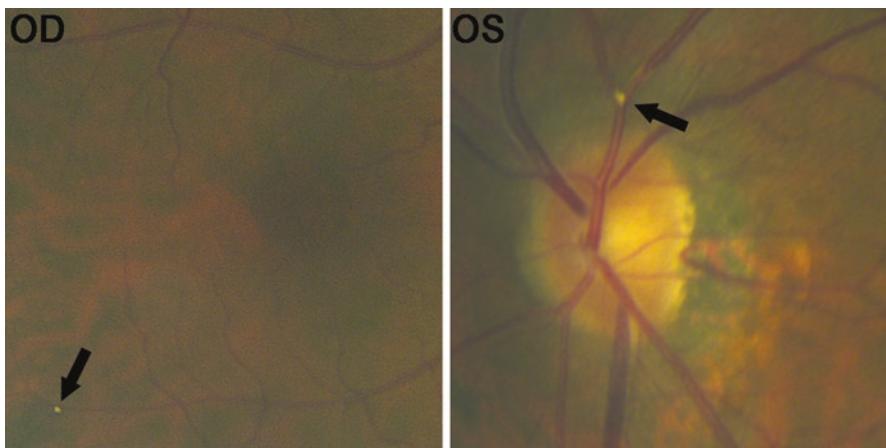


Fig. 7.12 Multiple bilateral retinal cholesterol emboli (arrows) from grade III aortic arch atheroma

Mechanisms of Vascular Transient Monocular Visual Loss

Vascular TMVL classically corresponds to transient retinal arterial ischaemia (also called retinal TIA). It may result from emboli in the ophthalmic artery or in the central retinal artery, from ocular hypoperfusion or, more rarely, from central retinal artery spasm [39]. Vascular TMVL resulting from optic nerve ischaemia is rare and is highly suggestive of giant cell arteritis, in which case the optic nerve is usually swollen. Rarely, TMVL may precede a central retinal vein occlusion, and dilated veins can be seen on fundoscopic examination. The description of the visual loss, its duration and ocular examination (particularly of the ocular fundus) are helpful in understanding the mechanism. Findings of retinal arterial emboli suggest a carotid, aortic arch or cardiac source of emboli. Retinal haemorrhages and dilatation of the veins suggest chronic ocular hypoperfusion and ocular ischaemic syndrome. Optic disc oedema suggests optic nerve ischaemia and should prompt immediate treatment and workup for giant cell arteritis. The association of TMVL and ipsilateral painful Horner's syndrome points to internal carotid artery disease and is highly suggestive of internal carotid artery dissection. Often, however, the ocular examination is normal and the patient is evaluated for all causes of retinal TIAs. Diffusion-weighted MRI is positive in 5% of patient with TMVL, and a major examination finding for the management of the patient can be found in 21% [41]. All patients over the age of 50 years require emergent workup for giant cell arteritis.

Binocular Transient Visual Loss

Binocular transient visual loss may result from bilateral ocular disorders or transient visual obscurations associated with papilloedema. It is, however, most suggestive of intracranial lesions involving the chiasmal and retrochiasmal visual pathways.

Ocular Causes of Binocular Transient Visual Loss

Episodes of binocular transient visual loss are usually not related to ocular causes of visual loss. Hyperglycaemia can produce lens changes and fluctuation in vision, and giant cell arteritis is the preferred cause of simultaneous bilateral retinal or optic nerve ischaemia in patients above 50 years of age. Malignant systemic hypertension with bilateral disc oedema and bilateral papilloedema from raised intracranial pressure are easily ruled out by fundoscopic examination.

Migrainous Visual Aura

Migrainous visual aura is the most common cause of transient binocular visual loss. The patient typically describes a scotoma extending over several minutes in a visual field, surrounded by jagged, luminous, shimmering edges. The scotoma can lead to a complete hemianopia and disappears gradually. A migrainous headache characteristically follows the scotoma, but some patients experience the visual aura of migraine without associated headache. The vision returns to normal within 20–30 min.

Occipital Transient Ischaemic Attack

Episodes of transient, complete binocular visual loss may represent a TIA in the distribution of the basilar or posterior cerebral arteries. A unilateral occipital TIA manifests as a transient homonymous hemianopia, whereas a bilateral occipital TIA manifests as a transient ‘cortical blindness’. As opposed to migraine, hemianopic events of ischaemic origin are typically sudden in onset and last only a few minutes. There may be associated headache, especially over the brow contralateral to the visual field loss, but the pain is usually coincident with the visual loss rather than following the visual loss, as in migraine. Other symptoms of vertebrobasilar ischaemia, such as vertigo, dizziness, imbalance, diplopia and bilateral extremity weakness, are often present. Diffusion-weighted MRI is positive in 12% of patients with transient homonymous hemianopia, and a major examination finding can be found in 36% with a high rate of atrial fibrillation (23%) [41].

Occipital Seizures

Occipital seizures typically produce brief binocular positive visual phenomena often described as flashing lights or bubbles. They usually last only a few seconds but are usually repetitive and relatively stereotyped in the same patient.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) can lead to acute bilateral visual loss lasting hours or days (Fig. 7.13). The MRI findings are classic and dramatic, and also resolve, but over a longer time than the visual loss [38].

Diplopia

As with transient visual loss, the first step in evaluating the patient who complains of diplopia is to determine whether the diplopia is monocular or binocular [1]. Unilateral monocular diplopia persists when one eye is covered and is present in one

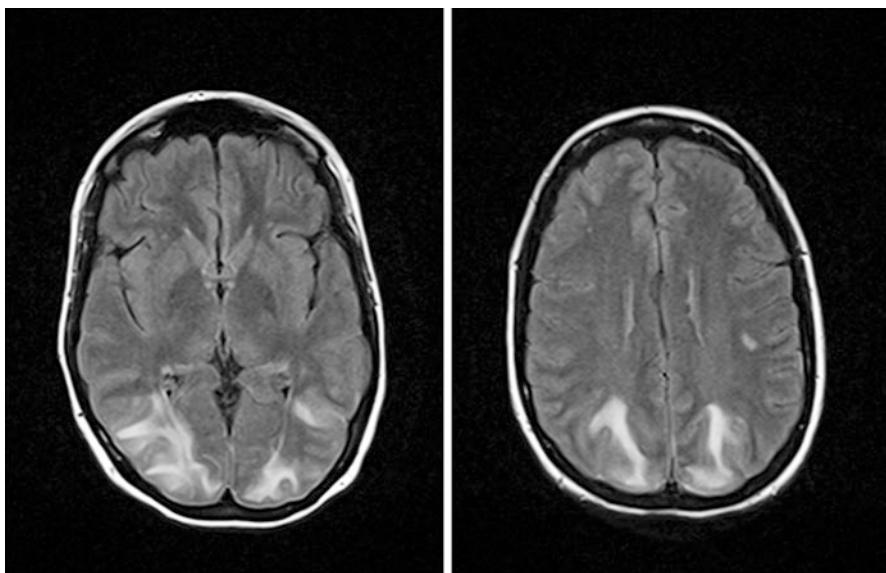


Fig. 7.13 FLAIR axial MRI of the brain showing bi-occipital hypersignals, suggesting posterior reversible encephalopathy syndrome in a patient with pre-eclampsia and bilateral visual loss

eye only. It is not a manifestation of a neurological disorder and results from altered transmission of light in the eye, most often from refractive or lens changes. Unlike patients with true diplopia, those with unilateral monocular diplopia often describe a ghost image or distortion of images, which improves when looking through a pinhole. Exceptionally, when monocular diplopia (or polyopia) is present in both eyes and does not improve when looking through a pinhole, it may reflect an occipitoparietal lesion.

Binocular diplopia disappears when either eye is covered and results from ocular misalignment. Acute binocular diplopia can result from disorders involving the extraocular muscles; neuromuscular junction (myasthenia gravis); cranial nerves III, IV and VI; cranial nerve nuclei (in the brain stem); or supranuclear and inter-nuclear pathways. Neurologists are familiar with various urgent disorders involving the brain stem that produce diplopia. In most cases, the associated neurological symptoms and signs allow immediate localization of the lesion. Isolated binocular diplopia is more difficult to localize and may still represent a neurological emergency.

Disorders Involving the Extraocular Muscles

Eye movement disorders that do not fit in with cranial nerve distribution, do not involve the pupil and are associated with other symptoms and signs localizing to the orbit suggest a primary lesion of one or more extraocular muscles [42]. For

example, in thyroid ophthalmopathy, there is uni- or bilateral subacute ophthalmoplegia, usually associated with proptosis and lid retraction (Fig. 7.14). In muscular dystrophies, there is slowly progressive bilateral ophthalmoplegia with ptosis. Acute extraocular muscle disorders include infectious, inflammatory and neoplastic orbital syndromes with proptosis, chemosis and visual loss, and patients with these rarely present to the neurologist. Venous orbital stasis from cavernous sinus fistulas or cavernous sinus thrombosis may produce diplopia secondary to enlargement of the extraocular muscles. The presence of an enlarged superior ophthalmic vein on

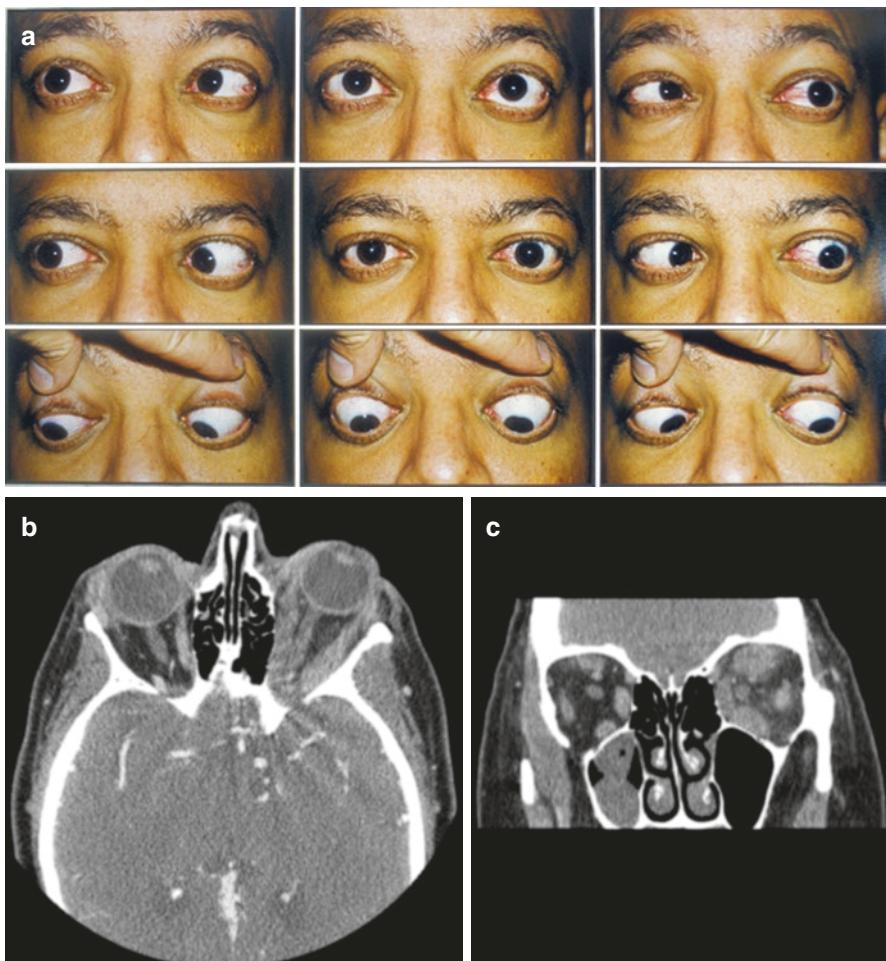
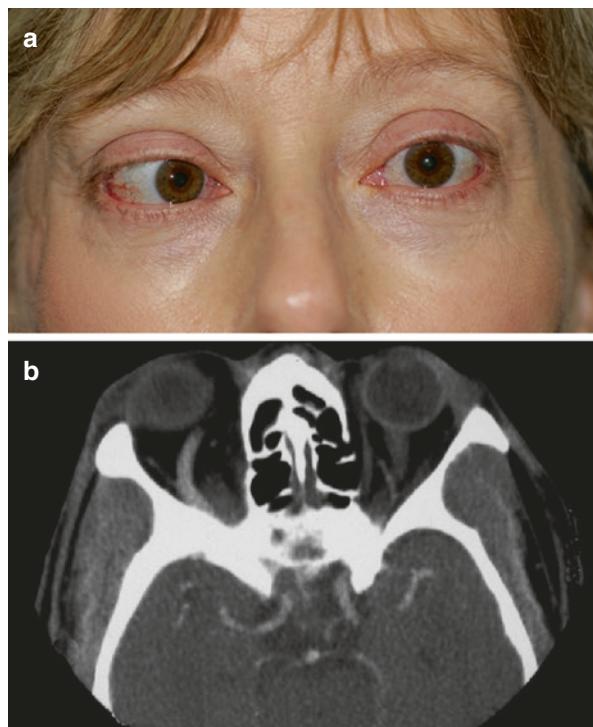


Fig. 7.14 Thyroid eye disease. (a) Abnormal eye movements and proptosis associated with lid retraction. Abduction and elevation of both eyes are decreased. (b) Orbital axial CT scan showing enlargement of the lateral and medial recti muscles (arrowheads). (c) Coronal reconstruction showing enlargement of all extraocular muscles on the left (arrowheads)

Fig. 7.15 Right VI nerve palsy and ocular redness revealing a dural carotid-cavernous fistula. (a) Eye movements showing an esotropia with limited abduction of the right eye. Note the right eye redness with dilatation of the episcleral vessels. (b) Axial CT scan of the orbits with contrast showing dilatation of the right superior orbital vein (arrowhead), highly suggestive of a carotid-cavernous fistula. The left superior ophthalmic vein (arrow) is normal



orbital imaging suggests a cavernous sinus process rather than an orbital syndrome (Fig. 7.15).

Neuromuscular Junction Disorders

Myasthenia gravis can mimic all extraocular movement disorders but is always painless, with the pupils of the patient being normal. The fluctuation of diplopia is a clue to this diagnosis [43]. However, myasthenia gravis is only an emergency when there are systemic symptoms suggesting generalized myasthenia gravis.

Ocular Motor Cranial Nerve Palsies

Isolated ocular motor cranial nerve palsies are usually due to lesions of the cranial nerve at the level of the cavernous sinus or in the subarachnoid space. Fascicular lesions most often produce other neurological symptoms and signs. In patients older than 50 years, it is important to verify that the CBC, platelets, ESR and CRP are normal since giant cell arteritis may manifest itself as isolated diplopia mimicking or related to an isolated cranial nerve palsy.

III Nerve Palsy

Isolated III nerve palsies may precede an aneurysmal rupture or reveal pituitary apoplexy. In patients older than 50 years who often have atheromatous vascular risk factors, the most common cause of isolated III nerve palsy is a non-arteritic microvascular III nerve palsy which does not require any specific workup. By definition, these patients have a pupil-sparing complete III nerve palsy in which all extraocular muscles innervated by the III cranial nerve are completely paretic and the pupil is normally reactive to light [44]. These patients present with complete ptosis, elevation, depression and adduction deficit of one eye. Younger patients, those with an incomplete (or partial) III nerve palsy, and those with pupil involvement require emergent imaging to check for compression of the III nerve (Fig. 7.16) [45, 46]. MRI, MRA and/or CTA are usually performed in the emergency setting, but catheter angiography may still be necessary when there is high clinical suspicion. Aneurysms (most often posterior communicating artery aneurysm) and pituitary apoplexy are life-threatening emergencies.

IV Nerve Palsy

Isolated IV nerve palsies rarely represent a neurological emergency. A IV nerve palsy results in binocular vertical diplopia increasing in down gaze, contralateral gaze and with ipsilateral head tilt [47]. The two most common causes include decompensation of a congenital IV nerve palsy and head trauma. Microvascular IV nerve palsies and compression are less common.

VI Nerve Palsy

Sixth nerve palsies result in binocular horizontal diplopia with limitation of abduction in the affected eye [47]. The VI cranial nerve is particularly sensitive to changes in intracranial pressure and fundoscopic examination to check for papilloedema, which would suggest raised intracranial pressure is essential (Fig. 7.17). Meningeal processes are also a classic cause of unilateral or bilateral VI nerve palsies, but non-arteritic microvascular unilateral VI nerve palsies are the most common cause of isolated unilateral VI nerve palsy in patients above 50 years of age.

Multiple Ocular Motor Cranial Nerve Palsies

Multiple cranial nerve palsies are highly suggestive of a cavernous sinus lesion when involving cranial nerves III, IV, VI and V₁ on the same side. The oculosympathetic fibres located around the internal carotid artery in the cavernous sinus are also often involved and produce an ipsilateral Horner's syndrome (Fig. 7.18). Skull base lesions and meningeal processes also produce multiple cranial nerve palsies.

When imaging is normal, disorders such as Miller Fisher syndrome (associated ophthalmoplegia, ataxia and areflexia), Guillain–Barré syndrome or even botulism should be suspected (Fig. 7.19) [48]. In all patients with presumed involvement of cranial nerves III, IV and VI and normal pupils, myasthenia gravis should be considered.

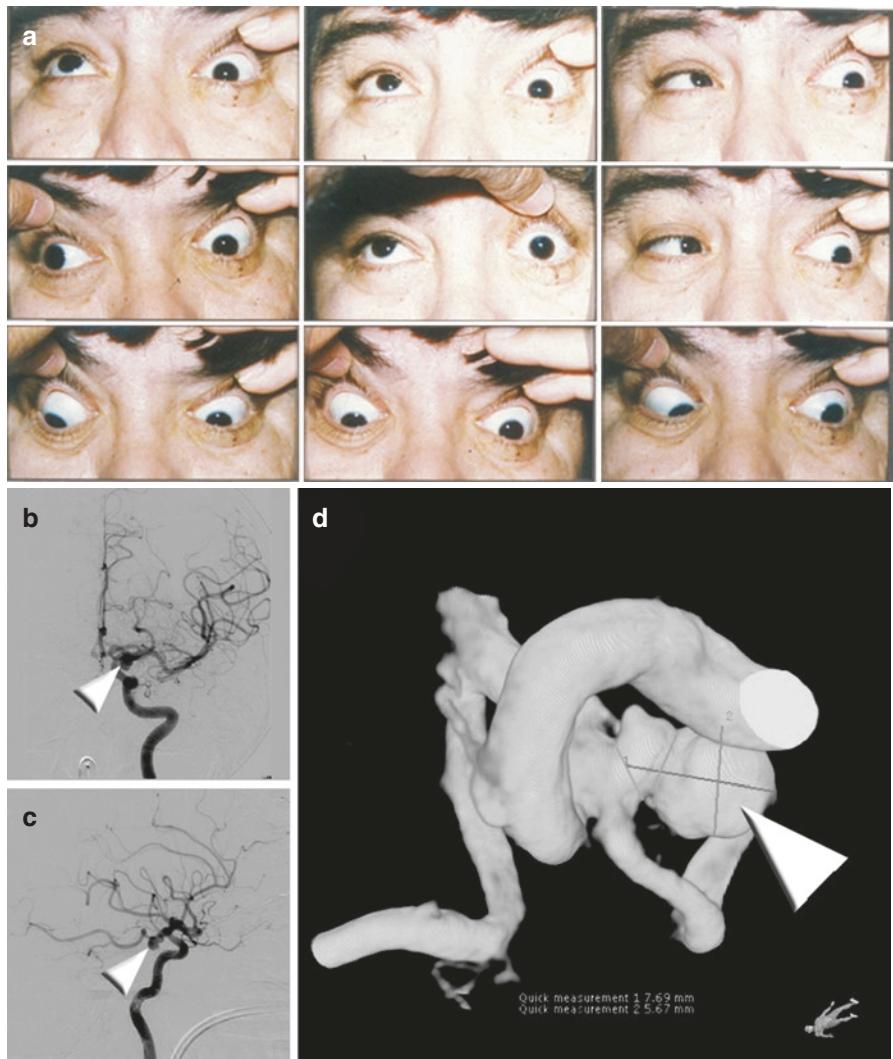


Fig. 7.16 Left III nerve palsy secondary to compression of the nerve by a left posterior cerebral aneurysm. (a) Eye movements showing left ptosis and limitation of abduction, elevation and depression of the left eye. Frontal view (b) and lateral view (c) of the catheter angiogram showing a left posterior cerebral artery aneurysm (arrowheads). (d) 3D reconstructions showing the aneurysm (arrowhead)

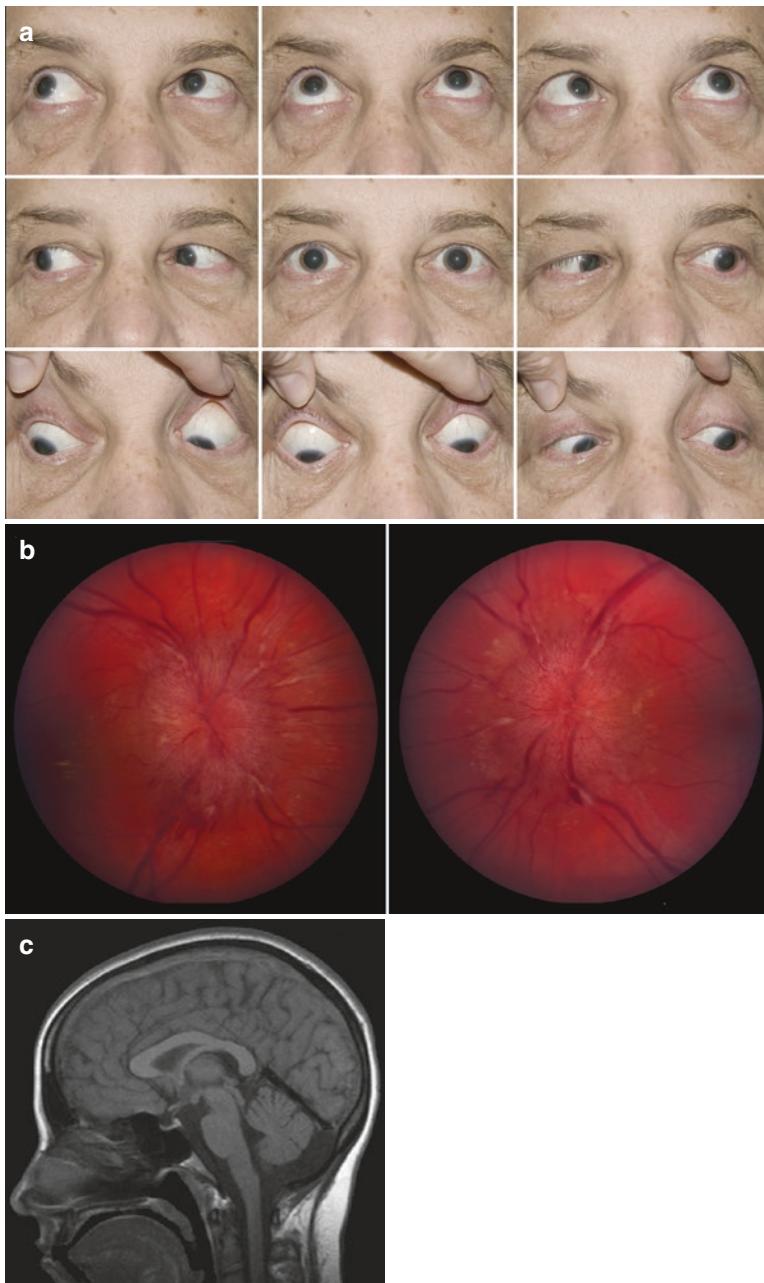


Fig. 7.17 Left VI nerve palsy and papilloedema related to raised intracranial pressure from cerebral venous thrombosis. (a) Eye movements showing a left abduction deficit. The pupils had been pharmacologically dilated. (b) Bilateral papilloedema. (c) T₁-weighted sagittal brain MRI without contrast showing a hypersignal within the superior sagittal sinus, suggesting subacute thrombosis

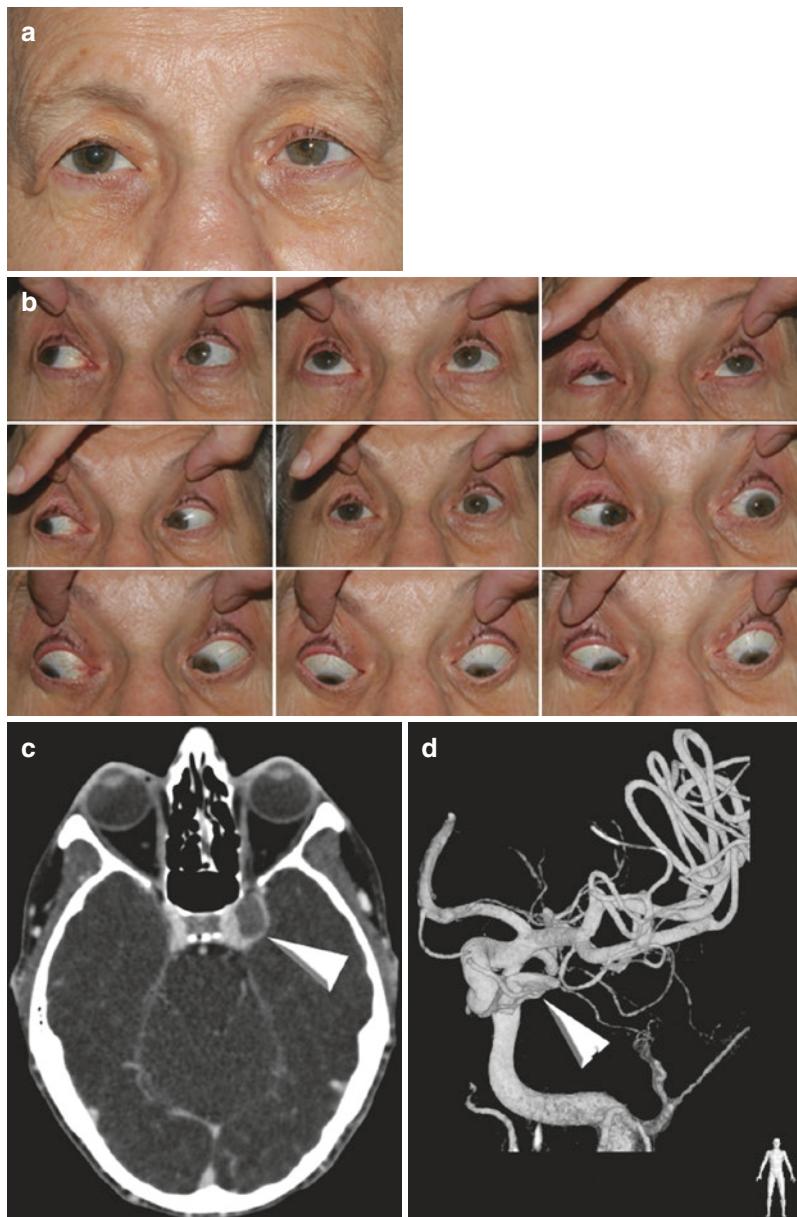


Fig. 7.18 Left VI nerve palsy with left Horner's syndrome related to a left carotid-cavernous aneurysm. (a, b) Eye movements showing decreased left abduction suggesting a left VI nerve palsy. Note the mild left ptosis and anisocoria with the left pupil being smaller than the right pupil, consistent with a left Horner's syndrome. (c, d) Angio CT with contrast demonstrating an aneurysm of the intracavernous part of the left internal carotid artery (arrowhead) responsible for the compression of the left VI cranial nerve and oculosympathetic fibres in the cavernous sinus



Fig. 7.19 Miller Fisher syndrome with bilateral ptosis, ophthalmoplegia and facial weakness. The eye movements are limited in all directions of gaze, and both pupils are dilated

Conclusion

Acute visual disturbances often bring patients to the emergency room. Visual loss and diplopia may represent neurological emergencies, and neurologists must be able to conduct a basic examination of visual function at the bedside and reliably examine the optic nerves with an ophthalmoscope. Collaboration between neurologists and ophthalmologists should facilitate immediate recognition of the underlying disorder and appropriate emergent management.

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Generalized Convulsive Status Epilepticus

8

J. M. K. Murthy

Introduction

Status epilepticus (SE) is a common neurological emergency associated with high morbidity and mortality [1]. SE is broadly classified based solely on the presence or absence of convulsions into convulsive SE (CSE) and nonconvulsive SE (NCSE). Early institution of appropriate treatment is associated with good outcomes.

Epidemiology

In the developed countries, the reported annual incidence rates ranged between 3.86 and 38 per 100,000 in children and 6 and 27 per 100,000 in adults [2]. The overall annual incidence of SE is 10–41 per 100,000 population [3–7]. Of the incidence cases of SE, generalized CSE (GCSE) accounts for 45–74% of all cases [3, 4]. Among the patients with CSE, 31–44% develop refractory SE (RSE) [8]. Of the patients with RSE, 10–15% fail to respond to third-line therapy (intravenous anesthetic agents) and are considered to have superrefractory SE (SRSE) [9].

Definition and Classification

Recently the Task Force of International League Against Epilepsy (ILAE) proposed the new conceptual definition of SE as follows: “status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizures termination or from the initiation of mechanisms which lead to abnormally prolonged

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seizure (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” [10]. This definition can also be extended to other forms of SE, focal SE with dyscognitive features and absence SE.

Time point t_1 indicates when treatment should be initiated (benzodiazepine responsive period), and time point t_2 indicates when long-term consequences may appear. The time point t_1 for tonic-clonic SE is 5' and 10' for focal SE with impaired consciousness. The time point t_2 for tonic-clonic SE and focal SE with impaired consciousness 30' and > 60', respectively. These time points should be considered as the best estimates currently available [10].

The Task Force of ILAE, taking into consideration the seizure semiology, proposed a classification of CSE (Box 8.1) [10]. Some of these clinical entities are age specific; thus this classification also guides the diagnostic work-up and treatment.

Status Epilepticus: Pathophysiology

SE occurs when mechanisms that normally abort seizures fail either because of excessive excitation or ineffective inhibition. With prolonged SE, receptor trafficking occurs with internalization of γ -aminobutyric acid A (GABA_A) receptors and upregulation of excitatory N-methyl-D-aspartate (NMDA) receptors. Both of these changes are pro-convulsants and sustain the SE [11, 12]. These changes lead to a mechanistic shift from GABA_A receptor-mediated inhibition to NMDA

Box 8.1: Classification of Convulsive Status Epilepticus [10]

- A. SE with prominent motor symptoms
 - A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
 - A.1.a. Generalized convulsive
 - A.1.b. Focal onset evolving into bilateral convulsive SE
 - A.1.c. Unknown whether focal or generalized
 - A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
 - A.2.a. With coma
 - A.2.b. Without coma
 - A.3 Focal motor
 - A.3.a. Repeated focal motor seizures (Jacksonian)
 - A.3.b. Epilepsia partialis continua (EPC)
 - A.3.c. Adversive status
 - A.3.d. Oculo-clonic status
 - A.3.e. Ictal paresis (i.e., focal inhibitory SE)
 - A.4 Tonic status
 - A.5 Hyperkinetic SE

receptor-mediated excitation. The increase in the number of inactive GABA_A receptors results in a significant reduction in the efficacy of antiepileptic drugs (AEDs) that target the GABAergic system, such as benzodiazepines, valproate, propofol, and phenobarbital. Ketamine, a noncompetitive NMDA receptor antagonist might play a role in treating RSE and SRSE by blocking NMDA receptor-mediated glutamatergic neurotransmission.

Clinical and Diagnostic Evaluation

Clinically GCSE is characterized by unresponsiveness and tonic, clonic, or tonic-clonic movements of limbs. The convulsive phase is followed by massive sympathetic drive. If the patient does not return to baseline within 10 min after cessation of clinical convulsive seizure, an EEG should be obtained to exclude nonconvulsive seizures (NCS) and/or NCSE [13]. Diagnostic work-up should be planned in parallel with treatment. Neurocritical Care Society guidelines for the evaluation and management of patients with SE are given in Box 8.2 [14].

Etiology

The etiology of SE is broadly divided into symptomatic (acute, remote, and progressive), genetic, and unknown [10, 15]. The prognosis of SE is the function of the underlying etiology, and acute symptomatic CSE is associated with higher

Box 8.2: Convulsive Status Epilepticus: Diagnostic Evaluation

Investigations in all patients

- Glucometer random blood sugar
- Monitor vital signs
- Head computed tomography (CT) scan
- Laboratory tests: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, antiepileptic drug (AED) levels
- Continuous electroencephalograph (EEG) monitoring in established SE and refractory and superrefractory SE

Investigations in specific clinical setting

- Brain magnetic resonance imaging
- Lumbar puncture
- Toxicology panel
- Laboratory tests: liver function tests, serial troponins, coagulation studies, arterial blood gas, and tests for inborn errors of metabolism

Box 8.3: Common Causes of Generalized Convulsive Status Epilepticus

Acute symptomatic

- Metabolic disturbances
- Hypoxia and anoxia
- Central nervous system and systemic infections including sepsis
- Prolonged febrile seizures in children
- Stroke: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis
- Traumatic brain injury
- Autoimmune encephalitis and paraneoplastic syndromes
- Drugs

Remote symptom

- Preexisting epilepsy(breakthrough seizures or antiepileptic drug discontinuation
- Chronic ethanol abuse in setting of ethanol intoxication or withdrawal
- Brain tumors: primary and metastatic
- Remote central nervous system pathology (e.g., stroke, abscess, TBI, cortical dysplasia)

Genetic epilepsies

Unknown cause

morbidity and mortality [4, 6]. In developed countries, acute stroke is the common cause of SE, more so in the elderly [16–18], whereas in developing countries, central nervous system (CNS) infections accounted for 28–67% of etiological spectrum [19–21]. No clear etiology can be identified in 20% of cases [22]. In persons with epilepsy, more than 50% of cases of SE are related to deliberate or accidental withdrawal of chronic AED treatment (Box 8.3).

Treatment

All contemporary treatment protocols for SE take a staged approach: Stage 1: early status epilepticus (time period t_1 , prolonged seizure 5'–10'); Stage 2: established status epilepticus (time period t_2 , for GTCS –10'–30'), Stage 3: refractory status epilepticus (–30'–60'), and Stage 4: superrefractory status epilepticus (>24 h) (Table 8.1) [23, 24].

Table 8.1 Pharmacotherapy algorithm in generalized convulsive status epilepticus

Stage of SE	Pharmacotherapy
Early SE	Benzodiazepines IV lorazepam (0.07 mg/kg, usually 4 mg), can be repeated if necessary once, OR IM midazolam (10 mg, in the elderly and in patients <50 kg 5 mg), can be repeated once after 10 min
Established SE	Non-sedating IV AEDs Phenytoin 18 mg/kg (range 15–20) IV bolus infusion at a maximum rate of 50 mg/min OR Fosphenytoin 15 mg PE/kg (range 15–20) IV bolus infusion at a maximum rate of 100 mg/min OR Valproate 30 mg/kg (range 15–20) bolus infusion at a rate of 3–6 mg/kg/min OR Levetiracetam 30 mg/kg (range 30–60) bolus infusion over 10 min OR Lacosamide 200–400 mg bolus infusion over 3–5 min
Refractory SE	cEEG monitoring—cIV anesthetic agents <i>Propofol:</i> 2 mg/kg IV bolus infusion (can be repeated if necessary) followed by cIV (5–10 mg/kg/h) dose to be adjusted to maintain burst-suppression pattern on cEEG OR <i>Midazolam:</i> 0.1–0.3 mg/kg IV infusion at a maximum rate of 4 mg/min followed by cIV (0.05–0.4 mg/kg/h) dose to be adjusted to maintain burst-suppression pattern on cEEG OR <i>Thiopental:</i> 100–250 mg IV bolus infusion over 20s with further 50 mg boluses every 2–3 min until seizure control followed by cIV (3–5 mg/kg/h) dose to be adjusted to maintain burst-suppression pattern on cEEG OR <i>Pentobarbital:</i> 5–15 mg/kg IV bolus, followed by cIV (0.5–3 mg/kg/h) dose to be adjusted to maintain burst-suppression on cEEG monitoring
Superrefractory SE	cEEG monitoring—cIV anesthetic agents (propofol/midazolam) + cIV ketamine (1–2 mg/kg IV bolus followed by cIV (up to 5 mg/kg/h) to adjust the dose to maintain burst-suppression on cEEG monitoring) Emerging treatments: Ketogenic diet, immunotherapy, epilepsy surgery, IV magnesium, treat the cause

Early Status Epilepticus

The first-line therapy of early CSE (prolonged seizure 5', time period t_1) is a benzodiazepine: lorazepam (Class I, Level A), midazolam (Class I, Level A), or diazepam (Class IIa, Level A) [14, 25]. Up to 40% of patients in early status cannot be controlled with benzodiazepines [26].

Established Status Epilepticus

If seizures continue despite benzodiazepine therapy, the patient is in established status epilepticus (Stage 2). Benzodiazepine-resistant CSE is typically treated with non-sedating IV AEDs: phenytoin/fosphenytoin (Class IIa, Level B),

phenobarbital (Class IIb, Level C), valproate (Class IIa, Level A), levetiracetam (Class IIb, Level C), and lacosamide (Class III, Level C) [14]. A recent meta-analysis assessed the relative effectiveness of IV phenytoin, phenobarbital, valproate, levetiracetam, and lacosamide in the treatment of benzodiazepine-resistant CSE. Clinically detectable cessation of seizure activity was the outcome measure. The meta-analysis revealed a mean efficacy estimate of 50.2% for phenytoin, 73.6% for phenobarbital, 75.5% for valproate, and 68.5% levetiracetam [27]. At present, based on the favorable tolerability profile and ease of use, levetiracetam and valproate are probably the preferred drugs in benzodiazepine-resistant GCSE over phenytoin/fosphenytoin and phenobarbital. The experience with lacosamide is limited [26].

Refractory Status Epilepticus

Despite the lack of formally accepted definitions, RSE is defined as “clinical or electrographic seizures that continue after initial treatment for SE, typically with a benzodiazepine and at least one other AED” [14, 28]. Risk factors predisposing to RSE include delay in receiving appropriate treatment and CNS infections, in particular encephalitis, metabolic encephalopathy, and hypoxia [29–31].

Patients with RSE require more aggressive treatment. They should be treated in intensive care unit, with mechanical ventilation. Hemodynamic support and metabolic monitoring are required. These patients require continuous EEG (cEEG) monitoring to monitor the efficacy of continuous intravenous (cIV) AEDs for seizure suppression, burst suppression, or complete EEG suppression [32]. Neurocritical Care Society guidelines suggest cEEG as mandatory in the management of RSE (Class I, level B evidence) [14].

When GCSE is refractory to non-sedating IV AEDs, most international guidelines advocate continuous IV (cIV) anesthetic drugs for induction of therapeutic coma. However, other non-sedating IV AEDs not used in the established stage of CSE should be considered before instituting therapeutic coma with anesthetic agents, particularly in the elderly. The rationale behind early escalation to therapeutic coma is to avoid development of neuronal injury from excitotoxicity [33] and benzodiazepine-resistance associated with prolonged seizures [34]. Most experience exists with cIV of anesthetic agents, pentobarbital, midazolam, and propofol [35], and the best comparative information comes from the systematic review which suggests no mortality difference among the three drugs [36]. There are no clear guidelines as to which anesthetic agent should be used first [35]. In patients with RSE, all non-sedating IV AEDs used during the stage of established SE should be continued, while treatment with cIV anesthetic agents is initiated. In most patients, this treatment regimen is sufficient to control the seizures.

Continuing EEG monitoring is mandatory during treatment of RSE with cIV anesthetic agents to guide drug titration to a target goal of electrographic seizure suppression [32]. Burst suppression and isoelectric background EEG have been shown to be accompanied by fewer recurrent seizures than simply stopping seizures [36]. Weaning of therapeutic coma is done after the patient has been in burst

suppression for 12–48 h (usually for 24 h) [14, 37]. If breakthrough seizures occur, anesthetic agent should be restarted, place the patient back into burst suppression, and cEEG is often continued for at least 24 h after cIV anesthetic agents are withdrawn.

The recent observational studies suggest that administration of anesthetic agents is associated with poor outcome independent of possible clinical confounders [38–41]. However, a more recent prospective study showed that the mortality was associated with increasing Charlson Comorbidity, Status Epilepticus Severity Score, etiology, and refractory SE. The use of therapeutic coma was associated with length of stay and related costs [42].

Superrefractory Status Epilepticus

Superrefractory status epilepticus is defined as “status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia” [23]. SRSE is not uncommonly encountered in neurological intensive care units. SRSE has been typically, but not exclusively, in two distinct clinical situations: (i) in patients with severe acute brain injury and (ii) in patients with no history of epilepsy, new-onset refractory status epilepticus (NORSE) [43]. Of the acute etiology, patients with encephalitis are more prone to SRSE [33, 44].

There is universal agreement that anesthetic agents are required as the backbone of therapy for SRSE, at least in the first few weeks. The choice is any of the three anesthetic agents. In SRSE while using cIV anesthetic agents, a combination of GABA agonist with NADM antagonist is proposed to avoid pure NMDA antagonist-induced neural damage [28, 35]. Ketamine appears to have a synergistic effect when combined with benzodiazepines [45, 46]. In a retrospective analysis, the overall SRSE resolution rate with propofol-ketamine combination therapy was 91%, the infusion rates ranged up to 145 and 175 mcg/kg/min, and the duration of the drug use ranged from 1 to 28 days (mean: 3.6 days) [47].

Several other therapies have been tried with variable success in patients who continue to be in SRSE despite of cIV anesthetic agents [23]. Most of these therapies are based on the mechanism of action in different phases of pathophysiology of SE (Box 8.4). However, the quality of evidence for most of the emerging therapies is low and mostly based on the efficacy in individual case reports or small case series. Treatment algorithms for SRSE are based on patient factors such as age, comorbidity, and cause of SE, if identified.

Of the emerging therapies in SRSE, there is cumulative evidence for ketamine. Ketamine is a noncompetitive antagonist of NMDA receptors and might act by blocking NMDA receptor-mediated glutamatergic neurotransmission. It also exerts neuroprotection by blocking glutamate-mediated NMDA receptor-induced neurotoxicity [48]. Ketamine is often considered as an alternative or add-on agent to anesthetic agent in the treatment of SRSE. Review of the studies on ketamine use in the treatment of RSE indicates that ketamine is a suitable anesthetic agent for the treatment of RSE and SRSE during prolonged seizures [23, 48–50].

Box 8.4: Some of the Emerging Novel Treatments in Superrefractory Status Epilepticus

- Ketamine (1–2 mg/kg bolus followed by cIV 0.6–5 mg/kg/h)
- Immunotherapy: Methylprednisolone and plasmapheresis
- Ketogenic diet (1:1–1:4)
- Magnesium (4 g bolus followed by infusion 2–6 g/h, target serum level ~3.5 mmol/L)
- Pyridoxine
- Hypothermia (35 °C for ~48 h, cooling blankets or endovascular)
- Resective surgery
- Neural stimulation: Vagal nerve stimulation, deep brain stimulation
- Electroconvulsive therapy
- CSF drainage

The use of ketogenic diet (KD) and modified Atkins diet (MAD) to control SRSE has been previously reported in case reports and small case series [23]. KD is a safe and feasible treatment for critically ill adults with RSE and SRSE when implemented appropriately [51, 52].

The rationale for the use of immunotherapy in SRSE is for two reasons: new-onset RSE (NORSE) can be the presenting feature of autoimmune encephalitis and the evidence that inflammation plays an important role in epileptogenesis, both in experimental animals and in humans [23]. Currently there is a possible place for immunotherapy in patients with NORES (Class IV) [53] and in patients with autoimmune epilepsy [54].

Convulsive SE: Complications

Systemic complications occur at every stage of SE. SE affects most organs of the body and can be due to persistent seizure activity or because of treatment. Close monitoring for these serious complications and early institution of appropriate interventions are very essential to reduce morbidity and mortality [55, 56]. The complications associated with SE include (i) early systemic complications (Table 8.2), (ii) complication related to treatment, and (iii) complications of prolonged ICU care [56].

Mortality

The overall reported in-hospital mortality in SE varied between 9.4 and 21% [57–59]. RSE is associated with high mortality and a significant morbidity; only about a third of patients return to their premorbid state [59, 60]. The prognosis of

Table 8.2 Convulsive status epilepticus: important early systemic complications

Hypertension	Hyperpyrexia
Hyperglycemia	Hypoxia
Acidosis	Cardiac arrhythmias
Takotsubo cardiomyopathy	Neurogenic pulmonary edema
Cardiac conduction abnormalities	Rhabdomyolysis and acute kidney injury

SRSE is rather poor, and the long-term mortality rates ranged between 39 and 50% [23, 61].

Conclusions

GCSE is a common neurological emergency associated with significant mortality and morbidity. Most often the treatment is not based on high-quality evidence except of benzodiazepines. Based on the favorable tolerability profile of levetiracetam and valproate, even though high-quality evidence is lacking, these drugs can be first-line drugs in established SE over phenytoin and phenobarbital. Treatment option in RSE is intravenous anesthetic agents. In SRSE ketamine in combination with anesthetic agents seems to be a better option. Other newer therapies in SRSE include ketogenic diet, immune therapy, epilepsy surgery, and others. The success of these therapies is quite variable. At this stage, therapeutic decisions are based on clinicians' preferences, patient factors such as age and comorbidity, and cause of SE, if identified [37].

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Headache in the Emergency

9

Aastha Takkar Kapila, Sudhir Sharma, and Vivek Lal

Introduction

Headache is by far the most common usual neurological complaint in general population. Given the spectrum of *benign* etiology to a *life-threatening* illness, it is a highly challenging symptom for a clinician in an emergency department (ED). The primary objective of the emergency clinician is often to determine whether the patient has a secondary headache attributed to an urgent medical condition requiring prompt therapy. In a busy emergency, it can be intimidating where a patient of severe tension-type headache presents with as severe a distress as a patient with subarachnoid hemorrhage. This may result in a tendency to over investigate with neuroimaging and additional lab investigations. These not only impose significant impacts on the patient's quality of life and healthcare economy but also cause unnecessary delays in appropriate treatment. In most instances, the clinician can accurately diagnose a patient's headache from history and careful clinical examination and determine whether neuroimaging or additional lab testing is indicated

The Burden of Headache

Headache accounts for between 1% and 4% of admissions to an emergency department [1–4]. More than two thirds of the headaches are benign primary headaches (PH) out of which migraine is the most common cause. PH constitutes a vast majority of patients presenting to emergency [5, 6]. Studies suggest that out of secondary

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headaches, 63% represent systemic infection, 4% are post-traumatic, 0.1% are due to space-occupying lesions, and 1% are due to subarachnoid hemorrhage (SAH) [7]. There is another major proportion of patients who are discharged with a diagnosis of *cephalalgia* or *headache—not otherwise specified*.

Etiology

Etiologically, headaches can be divided in two broad categories: primary and secondary. International Classification of Headache Disorders (ICHD), 3rd edition (beta version), gives an extensive document classifying various types of headache disorders [8]. Though such extensive classification is not usually required in routine clinical practice, it is useful when the diagnosis is uncertain. A simplified version is given in Table 9.1. While primary headaches have no organic disease as their cause, secondary headaches are caused by underlying organic disease.

The frequency of primary headache is lesser in EDs than in the general population [9]. The primary headaches in EDs represent the most severe and frequent attacks (treatment refractory and disabling migraine, cluster headache). The crucial elements for a differential diagnosis can be provided by the clinical characteristics of the headache and the associated neurological and somatic signs/symptoms.

Clinical Features

Most patients with headache have normal neurological and general physical examination, a thorough history is therefore crucial for accurate diagnosis. A careful history may allow the immediate diagnosis of primary headache syndromes avoiding

Table 9.1 ICHD-3 code diagnosis [8]

The primary headache disorders
1. Migraine
2. Tension-type headache (TTH)
3. Trigeminal autonomic cephalgia (TAC)
4. Other primary headache disorders
The secondary headache disorders
5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder
13. Painful cranial neuropathies and other facial pains
14. Other headache disorders

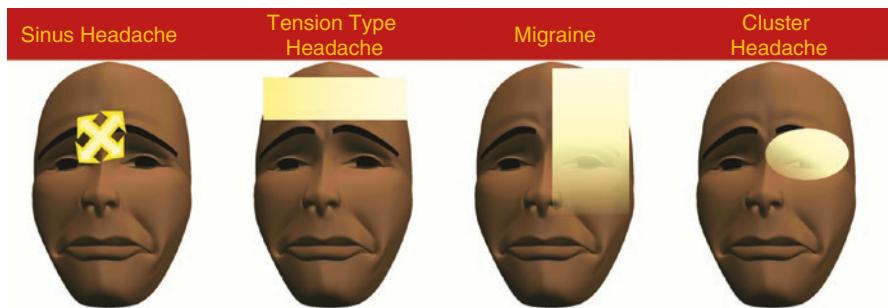


Fig. 9.1 Types of headaches depending upon the location

unnecessary investigations. The patients are asked to describe the nature of headache and the symptoms experienced before and during the headache. The pattern of onset, severity, frequency, duration, location, and distribution, and aggravating and relieving factors in detail are highly informative in making diagnosis. This information helps in identifying a primary headache disorder such as cluster headache (lacrimation and/or nasal congestion) or migraine with aura (e.g., scintillating scotomas, photophobia, phonophobia, nausea, etc.). Figure 9.1 describes the types of headaches depending upon their location. History of symptoms like diplopia, diminution of vision in a single eye, stiff neck, disorientation, rash, fever, eye pain, unilateral paresthesias, unilateral weakness, and incoordination points toward secondary headache disorder and requires further investigation.

A detail history is also necessary to identify “red flags” [10] that suggest an underlying organic disorder (Table 9.2). History of concurrent medical conditions and medications should be reviewed. Medications specially the “over-the-counter” medications (usually caffeine-containing analgesics) have been implicated as triggers for drug-rebound and nonspecific headaches. An organic cause of headache is more likely in an immunocompromised patient or a patient with other medical illness like cancer, HIV, hypertension, etc.

The physical examination should include a thorough general physical examination in addition to neurological assessment. Signs usually not encountered in neurology should be considered and actively sought. Thus, a skin rash, raised temperature, lymph node enlargement, and ear discharge should be carefully looked for. Recording vital signs and a thorough systemic examination are important. Complete neurological examination is essential and should focus on the areas identified abnormal during the history taking. Examination of higher mental functions, state of consciousness, examination of cranial nerves, pupillary reflexes, fundus examination, motor strength testing, deep tendon reflexes, sensory examination, cerebellar functions, gait testing, and signs of meningeal irritation (presence of neck rigidity, Kernig’s and Brudzinski’s signs) should be done in detail. The optic, oculomotor, trochlear, and abducens nerves (cranial nerves II, III, IV, and VI, respectively) should be done specifically [11–20].

Table 9.2 Red flags in the evaluation of acute headaches in adults [10]

Red flag	Differential diagnosis	Possible work-up
Headache beginning after 50 years of age	Temporal arteritis, intracranial space-occupying lesion	Erythrocyte sedimentation rate Neuroimaging
Sudden onset of headache	Subarachnoid hemorrhage, pituitary apoplexy, hemorrhage into a mass lesion or vascular malformation, intracranial space-occupying lesion (especially posterior fossa mass)	Neuroimaging Lumbar puncture if neuroimaging is negative ^a
Headaches increasing in frequency and severity	Intracranial space-occupying lesion, subdural hematoma, medication overuse	Neuroimaging Drug screen
New-onset headache in a patient with risk factors for HIV infection or cancer	Meningitis (chronic or carcinomatous), brain abscess (including toxoplasmosis), metastasis	Neuroimaging Lumbar puncture if neuroimaging is negative ^a
Headache with signs of systemic illness (fever, stiff neck, rash)	Meningitis, systemic infection, encephalitis, Lyme disease, collagen vascular disease	Neuroimaging Lumbar puncture ^b Serology
Focal neurological signs or symptoms of disease (other than typical aura)	Intracranial space-occupying lesion, vascular malformation, stroke, collagen vascular disease	Neuroimaging Collagen vascular evaluation (including antiphospholipid antibodies)
Papilledema	Intracranial space-occupying lesion, pseudotumor cerebri, meningitis	Neuroimaging Lumbar puncture ^b
Headache subsequent to head trauma	Intracranial hemorrhage, subdural hematoma, epidural hematoma, post-traumatic headache	Neuroimaging of the brain, skull, and, possibly, cervical spine

HIV human immunodeficiency virus

Adapted from Newman LC, Lipton RB. Emergency department evaluation of headache. *Neurology Clin* 1998;16:285–303

^aLumbar puncture may follow a negative neuroimaging procedure if suspicion of hemorrhage, infection, or malignancy remains high

^bSuspicion of specific central nervous system infections or intracranial hypertension (pseudotumor cerebri) warrants lumbar puncture with cerebrospinal fluid analysis and pressure measurement

The Thunderclap Headache [21]

Thunderclap headache is usually described as severe headache of instantaneous onset. Any thunderclap headache [even in a patient with a history of long-standing or recurrent headaches (such as migraine)] must be considered as secondary to a variety of causes, the foremost of which is subarachnoid hemorrhage. Figure 9.2 shows convexity subarachnoid hemorrhage in a patient of RCVS presenting with thunderclap headache. Associated neurological symptoms and abnormalities in general or physical examination may provide clues to some diagnoses. The

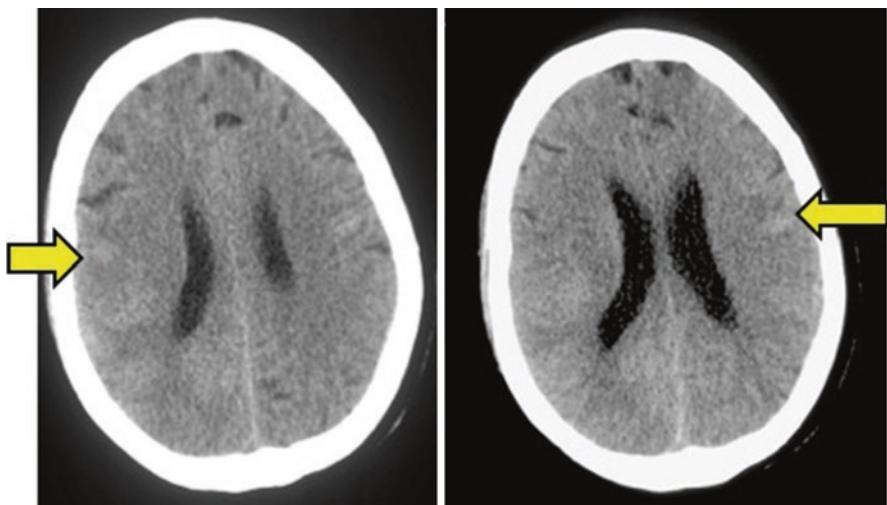


Fig. 9.2 Showing convexity subarachnoid hemorrhage in a patient presenting with thunderclap headache

absence of any associated symptoms and a strictly normal examination does not exclude the presence of sinister etiologies. An extensive diagnostic work-up is still needed.

Investigations

Neuroimaging

When to order computed tomography (CT) scanning or magnetic resonance imaging (MRI) is probably the most pertinent question while dealing patients with headache. The decision has significant impact on providing a quality and cost-effective care simultaneously. All patients with “red flags” should undergo imaging. CT scanning detects most abnormalities that may cause headaches that also are visualized on MRI.

ED handling neurological emergencies are usually equipped with computed tomography of head (and if required CSF analysis); it is being considered the first-line investigation in the diagnostic work-up of acute severe headache. It is important to assess the situations where further investigations may be required. Table 9.3 gives a list of causes that can be missed even after routine CT scans and CSF analysis. These conditions usually require further diagnostic work-up.

CT is generally preferred over MRI for the evaluation of acute subarachnoid hemorrhage (SAH), acute head trauma, and bone abnormalities.

MR imaging is more sensitive in the detection of posterior fossa and cervicomedullary lesions, cerebral venous thrombosis, subdural and epidural hematomas,

Table 9.3 Sowing differentials of Headache depending upon the imaging and CSF analysis [21]

	Causes usually detected by plain brain computed tomography (CT)
•	Subarachnoid hemorrhage (95% during the 24 h after bleeding)
•	Intracerebral hemorrhage
•	Intraventricular hemorrhage
•	Acute subdural hemorrhage
•	Brain infarct (after 3 h)
•	Tumor (third ventricle colloid cyst, posterior fossa tumor)
•	Hydrocephalus (aqueductal stenosis, Chiari type 1 malformation)
•	Acute sinusitis (diagnosis of exclusion)
	Causes detected by lumbar puncture after normal brain CT
•	Subarachnoid hemorrhage
•	Meningitis (bacterial or viral)
	Causes that may present with normal CT and normal or near normal cerebrospinal fluid
•	Dissection of cervical arteries (extracranial, intracranial, carotid, or vertebral)
•	Symptomatic aneurysm with mass effect (painful third nerve palsy)
•	Reversible cerebral vasoconstriction syndrome
•	Posterior reversible encephalopathy syndrome
•	Cerebral venous thrombosis (opening pressure may be high)
•	Pituitary apoplexy
•	Intracranial hypotension (opening pressure is low)
•	Brain infarct in patients in whom CT was performed within 3 h of onset
•	Temporal arteritis
•	Myocardial ischemia
•	Aortic dissection

neoplasms, meningeal disorders, white matter abnormalities, and infections. Pituitary pathology is more likely to be detected on a routine MR imaging study of brain than a routine CT scan. Acute headache can also be a presentation for cerebral venous sinus thrombosis and may necessitate a CT or MR venography in selected patients. While both CT and MRI are useful, clinical suspicion may at times help in choosing between the two, e.g., in the need to identify acute hemorrhage (CT scanning is preferred), need to evaluate the posterior fossa (MRI studies are preferred), general availability (CT scanning is more available), and cost and reimbursement issues (CT scanning is less expensive). Apart from these specific factors, MRI is usually considered more sensitive than CT scanning in identifying pathologic intracranial changes. Decision of neuroimaging is finally based on many factors including nature of complaints, associations, clinical examination, and triggering and relieving factors; a broad guide to need of neuroimaging is given in Fig. 9.3 [22]. Whether additional MRI studies help in identifying additional pathologies of potential benefit and help in improving over CT scanning in ED is still uncertain [23–25].

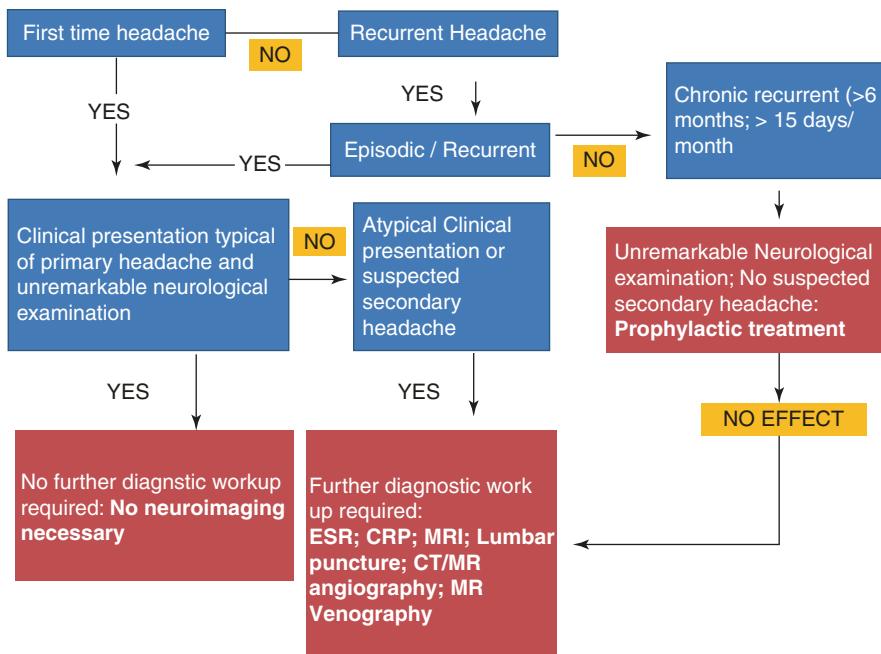


Fig. 9.3 Flowchart explaining decision-making regarding neuroimaging in headache

Lumbar Puncture

CT scan should be performed before a lumbar puncture for the evaluation of headaches. No prospective studies of safety of LP without performing CT have been conducted. Still, in the absence of any discernable focal neurological deficit or presence of any sign suggestive of increased intracranial pressure performing LP without a neuroimaging may be reasonable if indicated in emergent situations [10, 23]. A non-contrast CT scan should be performed, and if negative, it should be followed by a lumbar puncture to rule out subarachnoid hemorrhage within the first 48 h [23–25]. It is pertinent to note that a negative CT scan and lumbar puncture do not thoroughly rule out subarachnoid hemorrhage. In reality, it may take hours for blood to enter the CSF after the occurrence of hemorrhage. CSF should be specifically examined for the presence of xanthochromia if a relatively recent hemorrhage is suspected. Xanthochromia may be detected for at least a week after occurrence of subarachnoid hemorrhage. The presence of cellular reaction in CSF may help in identifying CNS infections, malignancies, and cellular abnormalities. The documentation of CSF pressure can help in diagnosing headaches due to increased or decreased intracranial pressure. Low CSF pressure headaches occur when CSF pressures are less than 90 mm of water, and increased CSF pressures occur if the CSF pressures are elevated greater than 200–250 mm of water [9]. Reduced CSF pressures can be caused by post-traumatic leakage of CSF (i.e., after lumbar

Table 9.4 Showing laboratory investigations indicated when specific cause for headache is suspected

Suspected etiology of headache	Blood tests
Suspected infectious disease	Complete blood counts, liver function tests, renal function tests, blood and body fluid cultures, HIV, and other serological assays as appropriate
Temporal arteritis, collagen vascular disease	ESR, CRP, rheumatoid factor, ANA
Antiphospholipid antibody syndrome	Lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein-1
Pituitary tumor	Hormone assays, endocrine studies

puncture or CNS trauma). Headaches related to increased intracranial pressure are seen in idiopathic intracranial hypertension, CNS infections, and CNS space-occupying lesions (i.e., tumor, infectious mass, hemorrhage).

Electroencephalography

The EEG is usually not contributory in the evaluation of headache [23, 26]. However this does not exclude the use of EEG to evaluate headache patients where the differentiation of symptoms suggestive of atypical migrainous aura and seizures is required. Also in patients with headache and episodic loss of consciousness, EEG may be useful. EEG does not help exclude an underlying structural lesion such as a neoplasm; CT or MR imaging is far mandatory. Hence, routine use of EEG in the evaluation of headache may not be rendered useful in general.

Laboratory Tests

Blood tests generally are not helpful for the diagnosis of headaches [23]. There are numerous indications however where secondary headaches are suspected in an appropriate clinical context and blood tests should be done in a specified clinical suspicion (Table 9.4).

Management

The immediate task before the clinician is to provide an accurate differential diagnosis and initiate any immediate treatment required. Cortelli P et al. [27] have proposed four “clinical scenarios” of patients with nontraumatic headache that correspond to common situations encountered in emergency department. These four scenarios may correspond to commonly encountered situations. Each of these scenarios may guide the physician selecting an appropriate diagnostic procedure and providing prompt and adequate treatment (Table 9.5).

Table 9.5 The four clinical scenarios proposed by the Italian multidisciplinary work-group for the management of nontraumatic headache in the ED [27, 28]

Scenario clinical features	Recommended diagnostic procedures
1. Adult patients admitted to ED for severe headache (“worst headache”)	
^a With acute onset (thunderclap headache)	^a Head CT must be performed
^a With neurological signs (or non-focal as decreased consciousness)	^a If the result of TC scan is negative or uncertain or of poor quality, lumbar puncture is indicated ^a If lumbar puncture shows no abnormality, the patient should be evaluated by a neurologist within 24 h
^a With vomiting or syncope at the onset of headache	
2. Adult patients admitted to ED for severe headache	
^a With fever and/or neck stiffness	^a Head CT and lumbar puncture must be performed
3. Adult patients admitted to ED for severe headache	
^a Headache of recent onset (days or weeks)	^a Head CT
^a Progressively worsening headache or persistent headache	^a Routine blood tests, including ESR and C-reactive protein must be performed ^a Neurological evaluation should be performed within 7days if tests are negative
4. Adult patients with a previous history of headache	
^a Complaining of a headache very similar to previous attacks in terms of intensity, duration, and associated symptoms	^a Evaluation of vital parameters, neurological examination, and routine blood tests are indicated ^a If tests are negative, the patient may be discharged from ED with indication to her/his general practitioner about the management of primary headaches and a prescription for a symptomatic headache treatment

^aReferring the patient to a neurological service or to headache center for long-term follow-up is recommended

Scenario 1

Adult patients admitted to ED for severe headache (“worst headache”):

- With acute onset (thunderclap headache)
- With focal neurological signs (or non-focal, like a decreased level of consciousness or with vomiting or syncope at the onset of headache)

In a patient who has experienced worst ever headache, the primary concern should be exclusion of aneurysmal subarachnoid hemorrhage. Early recognition of SAH is critical because of its potentially lethal character. When headache is associated with neurological signs, tumors, vascular malformations, stroke, vasculitis, pseudotumor cerebri, and meningitis also must be considered. In this group of patients, head CT is the first-choice examination. If CT is negative, or uncertain, lumbar puncture should be done.

Patients with headache and abnormal findings in a neurological examination should undergo emergent non-contrast CT scan, the same procedure being recommended for acute sudden-onset headache (Level B) [28].

Scenario 2

Adult patients admitted to ED for severe headache

- With fever and/or neck stiffness

In these patients, meningitis, encephalitis, and systemic infections have to be considered. Brain abscess, opportunistic infections in immune compromised patients, and aseptic or carcinomatous meningitis may also present similarly. Both CT and LP should be performed in these patients. Bacterial meningitis is a medical emergency and prompt treatment can improve outcome. Early administration of broad spectrum antibiotics (e.g., ceftriaxone 2g IV q12h) should be done even before completion of lab tests.

HIV-positive patients with a new type of headache should be considered for an urgent neuroimaging study (Level B) [28].

Scenario 3

Adult patients admitted to ED for:

- Headache of recent onset (days or weeks)
- Progressively worsening headache
- Persistent headache

In patients older than 50 years presenting with progressively worsening headache, a diagnosis of temporal arteritis (TA) and intracranial neoplasm should be excluded. Signs and symptoms suggestive of TA like jaw claudication, thickened and tender temporal arteries, etc. should be actively sought. In these patients, CT and routine blood tests, including ESR and CRP, should be performed.

Cases with a thunderclap headache that have negative findings in both CT scan and LP (normal opening pressure and negative CSF examination) do not need emergent angiography (Level C) [28].

Scenario 4

Adult patients with a previous history of headache complaining of a headache very similar to previous attacks in terms of intensity, duration, and associated symptoms

These patients usually belong to primary headache group and come to ED after failure of their usual symptomatic therapy. However careful history and clinical examination is still warranted to exclude more sinister causes. In these patients with no change in character of headache and no focal neurological signs and symptoms, the routine use of neuroimaging is not warranted. These patients can be treated symptomatically and discharged from ED to their primary care provider.

Treatment of Primary Headache Syndromes

Acute treatment of migraine, the most common primary headache syndrome, is directed at aborting the headache. The abortive (symptomatic) therapy of migraine ranges from the use of simple analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans or dihydroergotamine. Abortive treatments are usually more effective, given early during the headache. A large single dose tends to work better than repetitive small doses. Many oral agents may be ineffective because of poor absorption secondary to migraine-induced gastric stasis.

For a patient presenting in emergency department with acute attack of migraine, a migraine-specific therapy should be started. Options include triptans, dopamine antagonists, or ergot alkaloids.

Triptans

The serotonin 1b/1d agonists (triptans) are “specific” therapies for acute migraine since, in contrast to analgesics, they act at the pathophysiologic mechanism of the headache. Triptans can be given for patients with moderate to severe migraine. There are no efficacy data that definitively support the use of one triptan versus another. The choice of serotonin agonist should be individualized. The use of drugs with varied pharmacologic properties and delivery routes may help guide the choice. Sumatriptan offers a number of options for drug delivery. Naratriptan has been reported to have the lowest recurrence rate of all the serotonin agonists but has the slowest onset of action.

RizatRIPTAN is the fastest to take its action. Its dose must be adjusted downward in patients who take propranolol since propranolol may increase its levels by 70%. Almotriptan has lesser side effects than sumatriptan.

It should be noted that triptans are avoided in patients with familial hemiplegic migraine, basilar migraine, ischemic stroke, ischemic heart disease, Prinzmetal's angina, uncontrolled hypertension, and pregnancy. Also the first dose of the drug may be given under medical supervision for patients with risk factors but no known coronary heart disease (including men over the age of 40 and postmenopausal women and patients with controlled vascular risk factors such as diabetes mellitus, hypercholesterolemia, and hypertension). Combination with monoamine oxidase inhibitors is contraindicated with triptans other than eletriptan, frovatriptan, and naratriptan. Triptans should not be used within 24 h of the use of ergotamine preparations.

Dopamine Antagonists

Metoclopramide (IV), chlorpromazine (IV/IM), and prochlorperazine can be used as monotherapy for acute migraine episodes. Intravenous (IV) metoclopramide (10 mg) or prochlorperazine (10 mg) can be used for patients presenting with acute severe migraine in ED. They are specifically useful if headaches are associated with

severe nausea or vomiting. Diphenhydramine (20 mg IV every hour up to two doses) may be combined to prevent akathisia and other dystonic reactions.

Ergot Alkaloids

IV dihydroergotamine (DHE 45) 1 mg combined with IV metoclopramide 10 mg is a good alternative for patients with intractable severe migraine. In patients where metoclopramide monotherapy is ineffective, this can be of significant benefit. Parenteral DHE 45 should be avoided as monotherapy. DHE 45 is contraindicated in ischemic diseases involving cardiac, cerebrovascular, or peripheral circulations.

The American Headache Society convened an expert panel of authors who defined a search strategy and then performed a search of Medline, Embase, Cochrane database and clinical trial registries from inception through 2015. Identified articles were rated using the American Academy of Neurology's risk of bias tool. For each medication, the expert panel determined likelihood of efficacy. Recommendations were created accounting for efficacy, adverse events, availability of alternate therapies, and principles of medication action. Evidence-based treatment recommendations were created for adults with acute migraine who require treatment with injectable medication in an emergency department (ED). The highlights have been given in Table 9.6 [29].

Table 9.6 Acute management of migraine

Must offer (Level A)—None

Should offer (Level B)—To relieve the acute headache, intravenous metoclopramide/intravenous prochlorperazine/subcutaneous sumatriptan should be offered to adults who present to an ED with acute migraine (should offer—Level B). In the ED, sumatriptan may be less efficacious than intravenous antidopaminergics

May offer and may avoid (Level C)

Offer: Intravenous acetaminophen or intravenous acetylsalicylic acid/parenteral chlorpromazine/intravenous dexketoprofen/intravenous diclofenac/intravenous dipyrone/parenteral droperidol/parenteral haloperidol/intravenous ketorolac/intravenous valproate may be offered to adults who present to an ED with acute migraine (may offer—Level C)

Avoid: Intravenous diphenhydramine/intravenous hydromorphone/intravenous lidocaine/intravenous morphine/intravenous octreotide may be *avoided* in adults who present to an ED with acute migraine (may avoid—Level C)

No recommendation (Level U)—No recommendation could be made regarding the role of parenteral dexamethasone/injectable dihydroergotamine/injectable ergotamine/injectable ketamine/injectable lysine clonixinate / intravenous magnesium/intravenous meperidine/intravenous nalbuphine/intravenous propofol/parenteral promethazine/intravenous tramadol/intramuscular trimethobenzamide for adults who present to an ED with acute migraine (no recommendation—Level U)

Treatment of Secondary Headaches

Treatment of secondary headaches is directed at primary etiology such as appropriate antibiotics for headache attributed to infections like meningitis, surgical treatment of cerebral aneurysm causing subarachnoid hemorrhage, or evacuation of subdural hematoma. Regardless of the cause of headache, patient should receive adequate analgesia.

Conclusion

Understanding the clinical presentation of an acute headache is imperative for making a correct diagnosis, investigations, and management. This is to avoid both an over-investigative approach and errors.

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Risk Stratification and Management of TIA and Minor Stroke

10

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Introduction

Why Are Transient Ischemic Attack and Minor Stroke Important?

Together, transient ischemic attack (TIA) and minor stroke represent the largest group of cerebrovascular events, with one study estimating that over 80% of all stroke patients fall into this category [1]. With the advent of reperfusion therapies for acute ischemic stroke, systems of care have been streamlined such that patients with disabling or non-disabling deficits often present and are assessed very quickly after the onset of symptoms. Despite this, those with non-disabling deficits often fall into a therapeutic void since they are not considered eligible for thrombolysis or thrombectomy. This is particularly tragic since among patients considered too mild for thrombolytic therapy, up to one-third end up dead or dependent on being discharged from hospital [2, 3]. Furthermore, 15–30% of disabling strokes are heralded by non-disabling stroke or TIA, usually within the preceding 7 days [4]. Many studies have also demonstrated that after TIA or minor stroke, there is an approximately 10% risk of subsequent stroke within 90 days [5–13]. Functional disability may also affect about 15% of patients with TIA and minor stroke even in the absence of stroke recurrence [14]. Finally, as markers of vascular disease, TIAs predict an

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increased risk for all cardiovascular events and death in the longer term [5, 8]. Patients with mild cerebral ischemia represent an ideal target for therapy since they have a significant amount of tissue and function to safeguard in the face of an elevated early risk of major stroke.

Definitions: TIA or Minor Stroke?

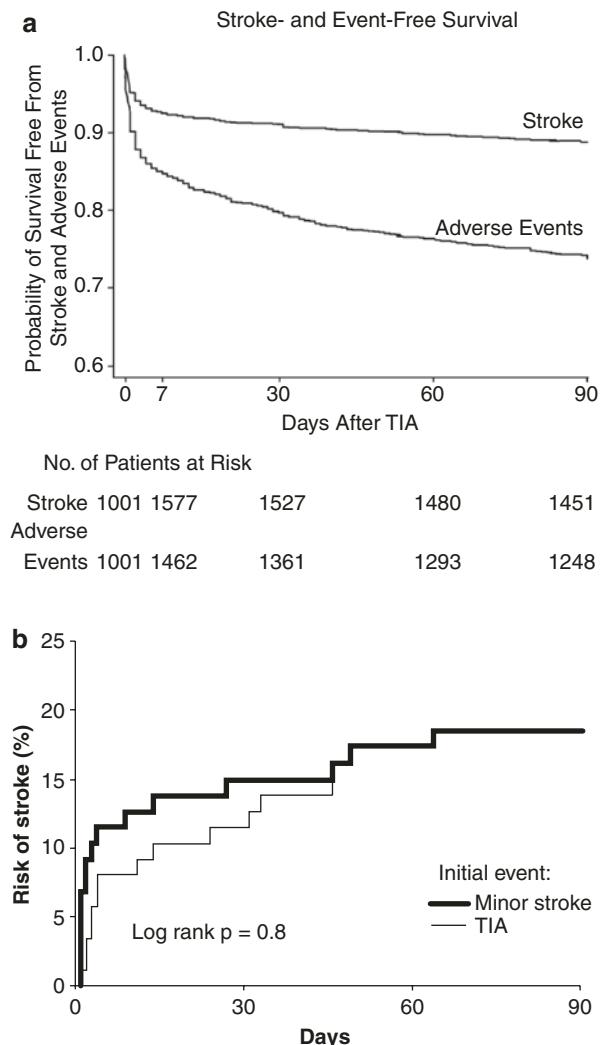
The classical definition of a TIA is “a sudden, focal neurological deficit that lasts for less than 24 h, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery” [15]. Since its inception in the 1950s, this definition has sparked debate because of the arbitrary nature of the 24-h time limit. Studies of TIAs have consistently found that many resolve within 30 min and most within 60 min, and if their duration exceeds 60 min, the large majority will go on to last over 24 h (and, therefore, be considered “strokes”) [16–19]. Increased understanding of cerebral ischemia using various imaging modalities, including CT and MRI, has supported the notion that even clinical symptoms resolving within 24 h can result in permanent injury to the brain parenchyma [20–26]. Kidwell and colleagues found that 48% of TIA patients had neuroanatomically relevant lesions on diffusion-weighted MR imaging (DWI) which may go on to represent areas of infarction [23]. Others have replicated these results [27, 28] and found that the presence of DWI lesions correlates with prolonged duration of symptoms, as well as speech and motor symptoms [21, 22].

Changes in the classical definition of TIA have been proposed so as to incorporate tissue imaging and the presence or absence of parenchymal injury [15, 25]. The American Heart Association (AHA) scientific statement of 2009 supports this approach, defining TIA as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction” [29]. This new tissue-based definition renders the duration of symptoms less important in distinguishing TIA from stroke and instead emphasizes the value of neuroimaging to identify tissue injury. Because patients with acute, focal neurological symptoms are increasingly assessed well within 24 h of onset, waiting for the symptoms to resolve by 24 h to make the diagnosis of TIA is unhelpful. In a clinical context, patients with mild or resolving symptoms cannot be readily differentiated from patients who will ultimately have a classical TIA. As a result, the practicality of distinguishing between TIA and minor stroke has been questioned, particularly given that they might share a similar prognosis [5, 15].

Risk of Recurrent Stroke After TIA and Minor Stroke

A cohort study of 1707 patients diagnosed with index TIA in the emergency department found that 10.5% returned with a stroke in the subsequent 90 days, of which half occurred in the first 2 days (Fig. 10.1a) [8]. In this study, the following clinical features were associated with a higher risk of stroke: age >60 years, diabetes,

Fig. 10.1 (a) Kaplan-Meier life table analysis of survival free from stroke and all adverse events (stroke, recurrent TIA, hospitalization for a cardiovascular event, and death) following TIA in the California TIA study [8]. (b) Cumulative risk of stroke following a TIA or minor stroke in the Oxford Vascular Study [5]



symptom duration >10 min, weakness, and speech impairment. A Canadian study of 2285 TIA patients produced similar findings, with a 90-day rate of stroke of 9.5% and a 1-year stroke risk of 14.5% [7]. A reanalysis of the Oxford Community Stroke Project (OCSP) showed an 8.6% risk of stroke within 7 days after TIA (Fig. 10.1b) [30]. Several other studies have confirmed that the risk of stroke after TIA ranges from 4% to 20% within 90 days of the event, with at least half of recurrent strokes occurring within 48 h [5, 11, 13, 30–32]. A recent analysis of TIA patients in the Oxford Vascular Study found that among patients who had a recurrent stroke within 30 days of their initial event, 42% suffered the recurrence within the first 24 h [33].

Risk Stratification After TIA and Minor Stroke: Clinical Tools

Risk Stratification Scoring Systems

Using a combination of patient variables and the clinical features of TIA, several risk stratification scores (California, ABCD) have been developed [8, 34]. The California and ABCD scores were combined to produce the ABCD² score [35]. The total ABCD² score, ranging from 0 to 7, relies on the summation of points associated with five clinical factors: age \geq 60 years [1 point]; blood pressure \geq 140/90 mmHg [1 point]; clinical features, unilateral weakness [2 points] or speech impairment without weakness [1 point]; duration of symptoms \geq 60 min [2 points] or 10–59 min [1 point]; and diabetes mellitus [1 point]. This score allows stratification of patients into high risk (score 6–7, 8.1% 2-day risk of stroke), moderate risk (score 4–5, 4.1% 2-day risk of stroke), and low risk (0–3, 1% 2-day risk of stroke) (Fig. 10.2).

Although the ABCD² score is a relatively simple risk stratification tool, it is limited in its ability to predict subsequent cerebral ischemic events, including those in the posterior circulation [36], and therefore clinical suspicion should continue to play an important role in determining urgency of investigations. In fact, a meta-analysis of the literature has underlined the unreliability of the ABCD² score in distinguishing patients with TIAs of low vs. high risk of recurrence [37]. The authors found that using a cutoff score \geq 4 misses 20% of patients with symptomatic carotid artery disease and that 39% of TIAs had a score < 4. These data further underline criticisms made by some authors regarding the lack of the score's diagnostic utility in differentiating cerebrovascular symptoms from mimics [38]. The importance of including vascular imaging investigations in prediction of stroke risk after TIA cannot be overstated as the presence of large-artery atherosclerosis and intracranial vessel occlusion is independently associated with stroke recurrence [39–41].

Fig. 10.2 Short-term risk of stroke by ABCD² score ($n = 4799$) [34]

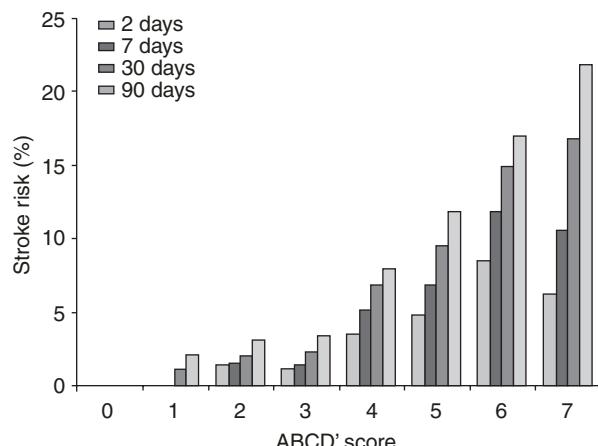


Table 10.1 TIA and minor stroke mimics and features suggesting alternative diagnoses

Diagnostic entity	Suggestive or confirmatory features
Migraine	History (slower-onset, positive symptoms, typical headache)
Subdural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage	Brain imaging, history (trauma, headache)
Mass lesion (e.g., tumor, abscess)	Brain imaging, history (progressive-onset, known cancer, immunosuppression, trauma, fever)
Presyncope/syncope	History, orthostatic symptoms, cardiac investigations
Seizure (often partial-onset)	History (slower-onset, positive symptoms), EEG, brain imaging
Peripheral vestibulopathy (benign paroxysmal positional vertigo, Menière disease, vestibular neuronitis)	History, physical examination (e.g., Dix–Hallpike, head impulse test), ENT evaluation, brain imaging
Delirium/metabolic encephalopathy	Non-focal symptoms, metabolic infectious workup, drug history, dementia
Exacerbation of previous stroke symptoms	Known previous stroke, intercurrent infectious/metabolic derangement, brain imaging
Anxiety/stress/somatization	History, inconsistent examination, suggestible symptoms

There are many nonvascular causes of transient neurological symptoms [35, 42] which may be mislabeled as TIA, including migraine with aura, seizure, syncope, peripheral vestibulopathy, subdural hematoma, tumor, and somatization/anxiety, among other diagnoses (Table 10.1) [27, 43–47]. It is therefore possible that the utility of risk scores to predict recurrent stroke stems primarily from their ability to identify true ischemic vascular events from more benign TIA “mimics” [48]. Such mimics are associated with a distinctly low rate of stroke or any vascular events at 1 year [49].

Baseline Neurological Assessment

There is evidence that in patients with a true classical TIA, the risk of a recurrent event is actually quite low, of the order of 1% [50]. However, even when patients are seen earlier than 24 h after the event, there seems to be prognostic value in whether or not the symptoms have completely resolved at the time of the first assessment [50]. In one study, patients deemed to be resolved after assessment by a stroke neurologist had a recurrent event rate of 6.6% versus 14.4% for patients who were not resolved [50]. On the other hand, an initially severe deficit demonstrating rapid and dramatic resolution (“spectacularly shrinking deficit”) may actually be a harbinger of subsequent deterioration [51, 52].

Early Identification of TIA/Minor Stroke Mechanism and Vascular Territory

Etiological classification appears to have value over and above the ABCD² scoring system, which may suffer from a ceiling effect [53]. Cerebral infarcts secondary to

underlying large-artery disease (primarily extracranial) are associated with the highest risk of early recurrence, almost eight times that of those due to small-vessel disease, which have the lowest risk. Cardioembolic events fall somewhere in between these two extremes [53, 54]. The magnitude of early stroke risk after TIA associated with large-artery disease was demonstrated in a study of patients with $\geq 50\%$ carotid stenosis, of which 20% went on to have a stroke in the 2 weeks prior to endarterectomy [55]. Furthermore, a post hoc analysis of the WASID trial revealed a 6.7% risk of stroke within 90 days of TIA in patients with symptom-relevant intracranial artery stenosis (50–99%) [56]. Higher recurrent stroke rates have also been found after posterior circulation TIAs in which atherosclerotic stenosis of the vertebrobasilar system was identified [57].

Risk Stratification After TIA and Minor Stroke: Neuroimaging Tools

Non-contrast CT

Non-contrast CT (NCCT) is currently the mainstay of investigation for TIA and minor stroke in most centers [11]. It is able to differentiate certain nonischemic mimics, such as subdural hematoma, parenchymal hemorrhage, and tumor. In one study, only 4% of TIA patients had evidence of infarct damage on CT [58], though other studies have found evidence of infarction in up to 20% of patients [26, 59, 60]. Strictly speaking, according to the new tissue definition of TIA, a NCCT with evidence of infarction should result in a diagnosis of stroke.

CT Angiography

The value of vascular imaging in TIA and minor stroke for identification of the etiology is well established, but emergent vascular imaging has only recently been evaluated for early risk stratification. Carotid imaging post-TIA is critical as symptom-relevant carotid stenosis $>50\%$ is associated with a higher risk of early stroke and the literature demonstrates a robust benefit from early carotid revascularization in these patients [61]. CTA allows for emergent identification of carotid stenosis [62], provides information regarding intracranial vasculature not visualized with ultrasound, is at least as accurate as MR angiography (MRA) [63, 64], and is comparable to digital subtraction angiography (DSA) [62, 65]. Prospective data from the CATCH study suggest that early assessment of intracranial and extracranial vasculature with CT/CTA predicts risk of recurrent stroke after a TIA or minor stroke [40]. The authors included 510 patients with TIA and minor stroke who underwent subsequent CT/CTA and MRI [40]. Although ongoing symptoms at first assessment, CT/CTA abnormalities, and positive DWI predicted recurrent stroke, only CT/CTA anomalies were significant predictors of repeated ischemia in the multivariate analysis [40].

A recent retrospective cohort study sought to determine predictors of early recurrent stroke in patients with neurologist-diagnosed TIAs and minor strokes (NIHSS 0–3) at two tertiary centers [66]. In multivariate models, predictors were large-vessel disease etiology as well as infarct on neuroimaging (CT or DWI-MRI). Other recorded variables were not associated with recurrence, notably the ABCD² score [66].

For these reasons, CTA has been proposed to be an essential initial imaging modality for all patients with suspected TIA or minor strokes in systems of care where this is feasible [67].

Multimodal MRI

MRI is superior to CT for demonstrating focal ischemic change, especially in small-volume lesions [68, 69], although MRI may be less readily available in most practice settings. DWI is particularly sensitive and specific in detecting ischemic damage and, as a result, has become the standard MRI sequence for confirming the presence of an acute or subacute cerebral infarct. A substantial proportion (40–60%) of patients with TIA have injury observed on DWI [22, 23]. Beyond helping to confirm the diagnosis of a vascular event in cases of diagnostic uncertainty, lesion pattern and location on DWI can alter the suspected anatomical and vascular TIA localization in over one-third of patients [23, 70]. Furthermore, early lesion characteristics on DWI sequence correlate well with etiological classification and allow for earlier determination of the mechanism of stroke [71, 72].

Hyperacute MRI in patients with TIA and minor stroke can also predict subsequent events and disability [73]. Patients with a DWI lesion have a higher risk of subsequent stroke and disability (modified Rankin Scale score ≥ 2) than patients without a lesion [73, 74]. Patients with the highest risk of a second ischemic event are those with both a DWI lesion and an intracranial occlusion, with much of this risk driven by intracranial vessel occlusion [73, 75–78].

Perfusion Imaging

Many academic centers have begun integrating computed tomography perfusion (CTP) in their initial imaging arsenal for patients with suspected TIA/stroke. As patients with stroke mimics represent one-fifth of those presenting with cerebrovascular-like symptoms [79], CTP was initially proposed as an imaging modality to differentiate stroke from its mimics [80]. Abnormalities in perfusion can be used to determine which patients have brain tissue not yet infarcted but at risk for ischemia (ischemic penumbra) if reperfusion is not assured. A prospective study of patients with symptoms consistent with anterior circulation TIA who underwent acute CTP found that one-third had focal perfusion abnormalities. These abnormalities were associated with motor symptoms, multiple episodes, ipsilateral symptomatic carotid artery stenosis or occlusion, large-artery atherosclerotic

etiology, and further in-hospital events [81]. As CTP can be easily integrated into initial CT/CTA imaging, it may be more readily available than MR perfusion in the acute phase in most settings [82]. Acute focal perfusion abnormalities in TIA/minor strokes have also been associated with higher degree of functional impairment at 3-month follow-up [83].

Cervical and Transcranial Doppler

Carotid Doppler studies are the mainstay of carotid imaging in many centers and provide sensitive and specific information regarding the presence of carotid stenosis. Transcranial Doppler (TCD) can identify intracranial proximal large-artery stenosis and allows for the detection of emboli [84]. Microembolic signals are most commonly observed in patients with unstable atherosclerotic carotid plaque [85, 86]. When emboli counts exceed 50 per hour, there appears to be a very high risk of impending stroke [87].

Combining Imaging and Clinical Risk Stratification Scores

The addition of two imaging elements (DWI lesion and intracranial vessel occlusion) to clinical factors in the ABCD² score allows for improved identification of TIA and minor stroke patients at high risk for functional disability (Fig. 10.3) [88]. Assessment schemes that integrate both clinical and imaging data might increase the efficient use of resources as patients could be triaged into low- and high-risk groups. Combining TIA mechanism, DWI status and clinical risk scores might offer a greater prognostic yield [89]. Table 10.2 summarizes the main clinical and radiological features that can help stratify the risk of stroke following a TIA or minor stroke.

Management of TIA and Minor Stroke

Urgent Assessment: How Soon and in What Setting?

Patients with TIA and minor stroke need to be assessed in an urgent manner by a physician experienced in managing stroke. Using clinical stratification tools such as the ABCD² score, patients with TIA and minor stroke can be triaged according to the expected risk of progression or recurrence of symptoms, and thus investigations and treatment can be tailored accordingly (Fig. 10.4). Some groups have abandoned the ABCD² score as a strict triage tool given its many limitations, instead emphasizing the presence or absence of motor and speech symptoms and the recentness of these symptoms (within or beyond the past 48 h) [97].

Despite this fact, the following algorithm can still be helpful in triaging patients with TIA and minor stroke. Patients with an ABCD² score of 6–7 (high risk)

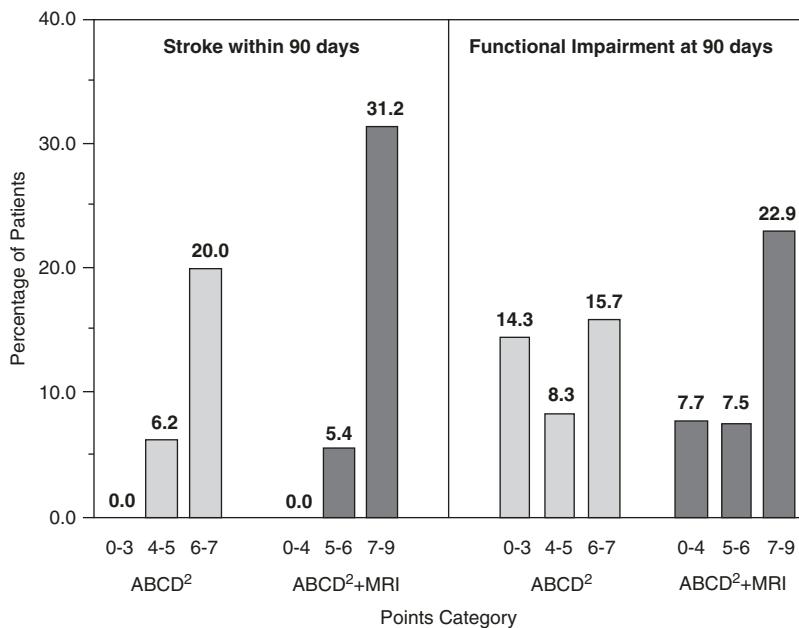


Fig. 10.3 Bar charts showing the percentage of patients who have a recurrent stroke within 90 days or have functional impairment at 90 days by the ABCD² and ABCD² + MRI scoring systems [75]

Table 10.2 Clinical and imaging characteristics of TIA and minor stroke and their relationship

with recurrent stroke risk

Low risk → High risk

Timing of event [7, 8, 11]	Weeks ago	Days ago	Hours ago
Age [8, 35]	<45 years		>60 years
Blood pressure in clinic/ED at event [35]	<140/90 mmHg		>140/90 mmHg
Diabetes mellitus [8, 35]	No		Yes
Patient symptoms [8, 35, 46, 47]	Dizziness/vertigo numbness	Monocular visual loss	Speech weakness
Duration of symptoms [35]	<10 min	10–60 min	>60 min
Frequency of events [46]	Many		One or few
Degree of initial clinical improvement [56, 57]	Initially very slight deficit improving		Spectacularly shrinking deficit that is initially severe
Extracranial internal carotid artery stenosis [6]	No stenosis		Severe stenosis or near-occlusion
Intracranial stenosis	Absent		Present
Intracranial occlusion [74, 80]	Absent		Present
DWI lesion [80, 81, 90, 91]	None	Solitary	Multiple
TCD emboli detection [92–94]	No MES/h	Any MES/h	50 + MES/h
Lacunar perfusion abnormality [95, 96]	No		Yes

DWI diffusion-weighted imaging, TCD transcranial Doppler, MES microembolic signals

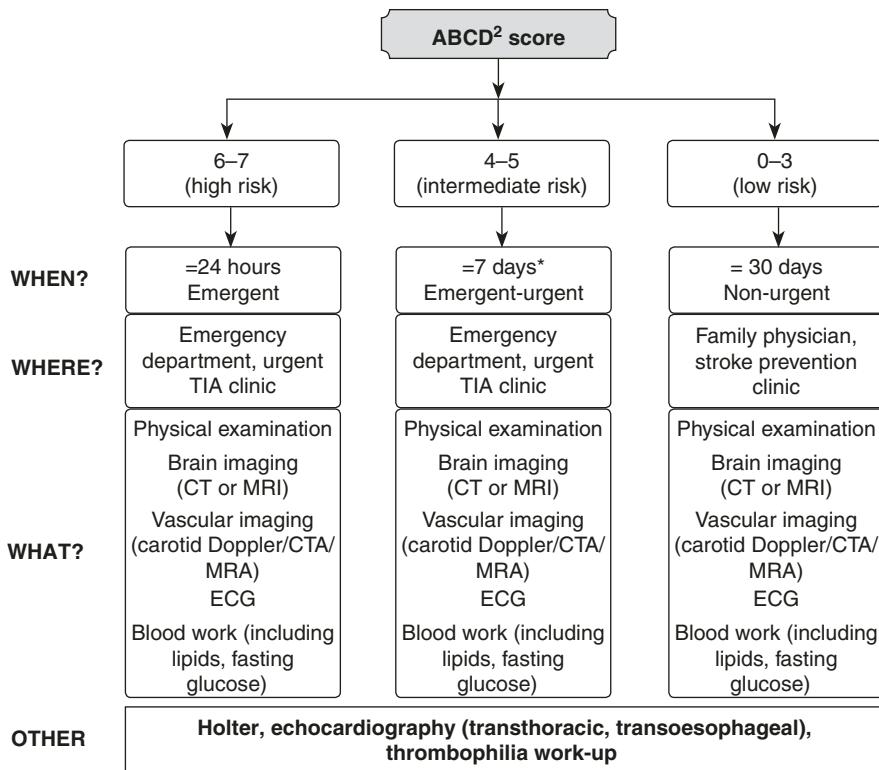


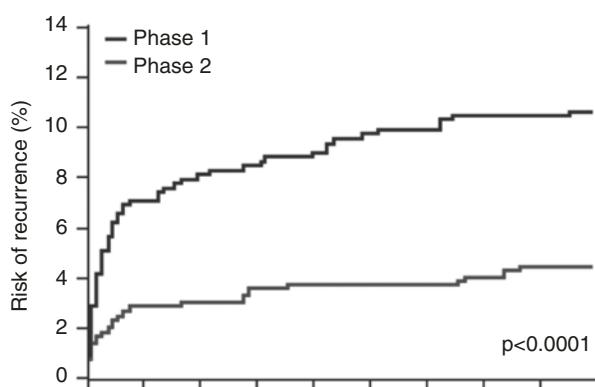
Fig. 10.4 Algorithm outlining the nature and timing of investigations after TIA according to risk stratification score. Clinical judgment should never be replaced by such an algorithm. (Asterisk) Patients with intermediate-risk scores generally go through brain imaging, ECG, and blood work at the time of their initial evaluation, with vascular imaging within 24 h, depending on clinical judgment and the resources available. Additional investigations may be pursued on the basis of the yield of initial testing, age of the patient, etc.

require parenchymal brain imaging with CT or MRI; cervical vessel (plus intracranial vessel) imaging with Doppler, CTA, or MRA; ECG; and relevant blood work (complete blood count, electrolytes, fasting glucose, lipid profile) within 24 h of the occurrence of their symptoms. Patients with scores of 4–5 (moderate risk) should have such investigations carried out within 7 days of the occurrence of symptoms, but in general practice, these patients are often assessed as rapidly as those with scores of 6–7. Finally, patients with scores of 0–3 (low risk) can have the aforementioned investigations performed within 30 days of the occurrence of symptoms. Further cardiac investigations, such as echocardiography, Holter monitoring, and, if indicated, prolonged telemetry, should be completed in most TIA patients, usually within 1 month of symptoms or sooner if a cardioembolic etiology is suggested by the patient's past medical history, clinical features, brain imaging, or ECG.

Investigations for patients at low risk can be organized on an outpatient basis. However, patients at high risk, and even those at moderate risk in whose case clinical judgment suggests a higher-risk profile, require investigations that must often be done expeditiously in an emergency department or on an inpatient basis. The concept behind urgent TIA clinics is that rapid access to appropriate evaluation, investigations, and therapy can be achieved in designated outpatient settings which might obviate the need for referral to the emergency department or admission in all but the most malignant cases. It should be emphasized that the use of risk stratification scores to triage TIA patients is not without limitations and that the ABCD² score has never been prospectively validated as a triage tool. Such algorithms, while guiding a general approach, should never supplant a physician's clinical judgment in managing individual patients.

Two studies have examined the impact of ultra-early assessment and management of TIA patients [49, 98]. The EXPRESS study from Oxford was a prospective "before versus after" analysis of the effect on the process of care and the outcome of more urgent assessment and immediate treatment in the clinic, as compared to the effect of subsequent initiation of management in primary care, among patients with TIA or minor stroke not admitted to a hospital [98]. Of 1278 patients, 634 in the first phase of the study were managed as per the "usual" local practice, with patients seen in the clinic within a median of 3 days after referral from primary care, and treatment suggestions made for the primary care physician to implement later. In the second phase, 644 patients were seen in the clinic more rapidly (median delay from referral <1 day), and treatment and investigations were initiated at this first visit by the stroke neurologist. The 90-day risk of recurrent stroke fell from 10.3% in the first phase to 2.1% in the second phase (adjusted hazard ratio 0.20, 95% CI 0.08–0.49; $p = 0.0001$), without an increase in intracerebral hemorrhage or other bleeding (Fig. 10.5). In both phases, patients were loaded with aspirin, clopidogrel, or both, started on simvastatin, and treated with perindopril, with or without indapamide depending on whether the systolic blood pressure was >130 mmHg. Anticoagulation was started, if appropriate, and patients were referred for carotid endarterectomy (CEA) if they had $\geq 50\%$ stenosis on the appropriate side. Apart from more frequent

Fig. 10.5 Risk of recurrent stroke after medical attention was first sought for all patients with TIA or stroke in the whole study population in Phase 1 versus Phase 2 of the EXPRESS study [77]



use of a 30-day course of dual antiplatelet therapy and increased prescription of two antihypertensive agents, the treatment employed in both phases of this study did not differ significantly. Most likely, the improvement in outcomes resulted not from the novelty of the therapies but from the rapidity with which they were initiated.

The second study to examine the value of a new system of care for TIA patients was the SOS-TIA study from Paris [49]. In this study, a 24-h hospital-based TIA clinic was established and the process of care and outcome events were measured. Over almost 3 years, 1085 patients with resolved events were seen, about half within 24 h of the occurrence of symptoms. The patients were examined, and brain, vascular, and cardiac imaging and treatment were initiated within 4 h of presentation. As in EXPRESS, the treatment included antiplatelet agents, statins, blood pressure reduction, anticoagulation, and carotid revascularization, as appropriate. About 25% of the patients required admission. The 90-day stroke rate was 1.24%, as compared with a rate of 5.96% predicted from ABCD² scores.

Both studies reinforce the concept that the existing therapies for the prevention of secondary stroke are effective if started very early after TIA. These therapies include (1) antiplatelet agents, (2) antihypertensive agents, and (3) lipid-lowering agents. More specific therapies include (1) anticoagulation, if mandated by the TIA mechanism, and (2) early revascularization, particularly CEA in the setting of appropriate ipsilateral carotid stenosis (>50%).

Treatment Approaches

Acute Antiplatelet Therapy

The mainstay of medical management in etiologically undifferentiated TIA patients remains oral antiplatelet therapy. This can either be aspirin (ASA), clopidogrel (Plavix), a combination of both, or combination aspirin/extended-release dipyridamole (Aggrenox). Regardless of which agent is used, it should be initiated as soon as possible after the exclusion of intracranial hemorrhage with an oral loading dose (ASA 160–325 mg, clopidogrel 300 mg, or Aggrenox one tablet [50/200 mg], in addition to 160 mg of ASA). Aspirin was studied in the acute phase of stroke in the International Stroke Trial and the Chinese Acute Stroke Trial [99, 100]. In both trials, a loading dose of ASA (160–300 mg) was given to patients within 48 h of their event. A pooled analysis of both studies demonstrated that ASA prevented an outcome of dependence or death at 6 months in 13 of every 1000 patients treated, despite a slight increase in hemorrhagic events [101]. Few patients in these trials were enrolled with TIA or minor stroke as index events, however.

The other common antiplatelet agents, clopidogrel and Aggrenox, have not been studied as monotherapy in the acute phase after TIA or minor stroke. Major trials of combination aspirin/extended-release dipyridamole, ESPS-2, ESPRIT, and PRoFESS, included patients who had had ischemic events up to 3 or 6 months prior to enrolment [90, 102, 103]. The trials of clopidogrel monotherapy in secondary stroke prevention include MATCH, PRoFESS, and CAPRIE; the last study actively excluded patients who had symptoms within 1 week of assessment [92, 103, 104].

Given the superiority of combination aspirin/extended-release dipyridamole over ASA alone in ESPS-2 and ESPRIT for the prevention of long-term secondary stroke, guidelines suggest that the use of this agent may be reasonable in TIA patients [93, 94].

Clopidogrel is also considered a reasonably good first-line agent in the acute phase after TIA, primarily extrapolating from MATCH, PRoFESS, and the acute coronary syndrome literature [93]. It is also indicated in patients with an allergy to ASA [105]. Either clopidogrel or combination aspirin/extended-release dipyridamole may be considered in patients who have had an event despite already being on ASA (“aspirin failures”) [93].

Combination antiplatelet therapy, comprising loading doses of ASA and clopidogrel, is also an approach employed in certain cases of TIA, often in patients judged to be at high risk for progression or recurrence. This approach may be particularly suited to patients with large-artery atherosclerosis, particularly extracranial carotid stenosis with presumed unstable plaque.

Three randomized trials have assessed dual antiplatelet therapy (ASA and clopidogrel) in the acute phase after TIA: FASTER, CARESS, and CHANCE [105, 106]. FASTER was a randomized, double-blind, placebo-controlled pilot study, in a factorial design, of whether clopidogrel and simvastatin started within 24 h of the onset of symptoms and continued for 90 days would reduce the risk of stroke after TIA or minor stroke [106]. Patients in the treatment arm were given a 300 mg loading dose of clopidogrel, followed by 75 mg daily, and simvastatin at an initial dose of 40 mg, followed by 40 mg daily. All patients were also loaded with 162 mg of ASA, that is, if they were not already taking it. Among patients receiving clopidogrel, there was a trend toward benefit (RR 0.7, 95% CI 0.3–1.2). When given with clopidogrel, simvastatin seemed to attenuate the potential benefit of the antiplatelet agent. In patients receiving clopidogrel and ASA versus those on ASA alone, there was an increased risk of symptomatic (3.5% vs. 0%, $p = 0.03$) and asymptomatic (30.8% vs. 13.9%, $p = 0.0001$) hemorrhage.

CARESS, a randomized, double-blind study of 107 patients with recently symptomatic carotid stenosis $\geq 50\%$ and microembolic signals on TCD, compared ASA monotherapy with combined aspirin and clopidogrel [105]. Approximately 60% of patients had TIA as their index event, and about 40% were randomized within 7 days of the event. The primary outcome was persistence of asymptomatic microembolic signals on TCD after 7 days of treatment. This occurred in 43.8% of patients on dual therapy, as opposed to 72.7% of those on ASA alone ($p = 0.0046$). There were four recurrent strokes in the monotherapy group, compared to none in the combined therapy group, although the study was not powered to look at clinical outcomes.

The authors of the FASTER trial also conducted a meta-analysis of long-term secondary prevention trials using dual antiplatelet therapy in which a subset of patients was enrolled early after their qualifying event. From the MATCH, CHARISMA, and CARESS trials, 35 patients were identified who were randomized to combined ASA plus clopidogrel versus monotherapy within 24 h of their index event [92, 105, 107]. The meta-analysis was driven primarily by the 392

patients in FASTER and demonstrated a borderline significant reduction in combined 90-day risk of death, stroke, TIA, or acute coronary syndrome for patients receiving dual antiplatelet therapy (Fig. 10.6). However, MATCH and CHARISMA found that long-term combined aspirin and clopidogrel therapy after stroke and TIA is not beneficial and is potentially harmful [92, 107].

A more recent randomized double-blind control trial evaluating dual antiplatelet therapy trial in a Chinese population, CHANCE, randomized patients with a minor stroke (NIHSS ≤ 3) or TIA and an ABCD² score ≥ 4 to receive either combination clopidogrel and aspirin with initial bolus for 3 weeks and then clopidogrel monotherapy or aspirin monotherapy [108]. Primary efficacy outcome at 90 days evaluated the presence of new stroke, either ischemic or hemorrhagic, and primary safety outcome was the presence of moderate to severe hemorrhage. Results indicated a significant reduction in stroke at 3 months HR 0.68 (0.57–0.81) $p < 0.001$ in the group treated with combination therapy, notably a significant reduction in ischemic stroke with no increase in the incidence of intracerebral hemorrhage. This resulted in an absolute risk reduction of 3.5%. There was, however, a worrisome trend toward increased overall bleeding with combination therapy. There is debate in the neurovascular community as to whether these results can be generalized to other non-Chinese populations given the well-established differences between ethnicities—higher prevalence of intracranial atherosclerosis and genetic polymorphisms that affect the metabolism of clopidogrel in Chinese [109], for example. To answer this question, the North American POINT trial is currently underway, its primary objective being to determine whether early combination therapy is protective against recurrent vascular events [110]. Similarly, the British TARDIS (Triple

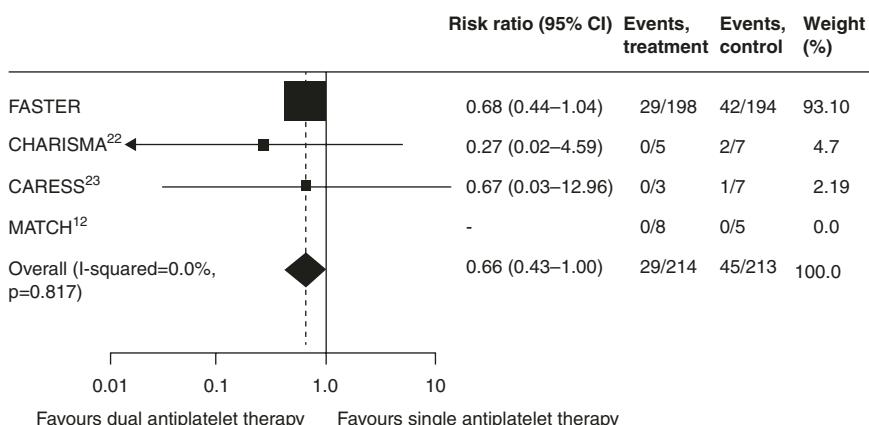


Fig. 10.6 Fixed-effects meta-analysis of 90-day risk of tertiary efficacy outcome with antiplatelet monotherapy versus combined aspirin and clopidogrel in the acute phase after TIA (Tertiary outcome was combined outcome of stroke, TIA, acute coronary syndrome, and all-cause death in patients enrolled within 24 h of the onset of stroke or TIA. Note that the X-axis is a logarithmic scale.) [97]

Antiplatelets for Reducing Dependency after Ischemic Stroke) trial is also currently recruiting acute TIA patients and will compare management with the current standard of care to 30-day triple antiplatelet therapy with aspirin, dipyridamole, and clopidogrel [111].

The newer antiplatelet agent ticagrelor has not been shown to provide additional benefit over aspirin alone in this patient population (SOCRATES) [95].

Another heavily debated point surrounds the treatment strategy for patients already taking aspirin when presenting with new TIA/stroke (so-called ASA failures). Patients from a large South Korean stroke registry with acute noncardioembolic stroke who were taking ASA at the time of symptom onset were enrolled and divided into three groups according to subsequent antiplatelet strategy—maintaining ASA, switching to non-aspirin antiplatelet agents, and adding another antiplatelet agent to aspirin [96]. In this nonrandomized study, there was a reduction in composite vascular event primary end point in the group that switched to a non-ASA agent (HR 0.50; 95% CI, 0.27–0.92; $P = 0.03$) and in the one that added a second antiplatelet agent (HR 0.40; 95% CI, 0.24–0.66; $P < 0.001$). However, an analysis of patients with lacunar stroke from the SPS3 trial taking ASA at trial entry did not find any benefit of adding clopidogrel over remaining on ASA alone [112]. Although there is no clear evidence to strictly guide management in this scenario, dual antiplatelet therapy is favored in the acute phase by some stroke specialists, but concern over long-term hemorrhagic risk has limited the duration of dual therapy to between 3 weeks and 3 months.

Acute Anticoagulant Therapy

Although the benefits of oral anticoagulation for the prevention of secondary stroke in patients with certain subtypes of cardioembolic stroke are well known, acute anticoagulation after TIA or minor stroke has never been formally studied. The current guidelines do not support the use of unfractionated or low-molecular-weight heparin in acute stroke to prevent early recurrence or stroke progression [91, 94]. The primary concern with urgent anticoagulation is bleeding, both intracranially and extracranially. Intracranial bleeding is a greater concern among patients with severe strokes in whom the volume of ischemia is larger. In patients with TIA and minor stroke, who have minimal or no infarction on imaging, it may be that the risk of ICH with acute anticoagulation is distinctly low. On the basis of this assumption, TIA and minor stroke patients with a clear indication for anticoagulation (i.e., atrial fibrillation) could be rapidly anticoagulated using low-molecular-weight heparin or unfractionated heparin without a bolus as a bridge to a therapeutic INR (2.0–3.0) on warfarin or started quickly on one of the newer direct oral anticoagulants (dabigatran, rivaroxaban, or apixaban). However, the pivotal direct oral anticoagulant trials did not include patients in the acute phase after minor stroke or TIA [113–115].

In a study of danaparoid after stroke, the subgroup of patients with stroke due to large-artery disease was the only one in which anticoagulation was demonstrated to have benefits [116]. One might surmise that the benefit of anticoagulation may be even greater in patients with visualized intraluminal thrombus (either secondary to

plaque rupture, thromboembolism, or dissection), though this has not yet been shown.

Finally, combination therapy with antiplatelet agents and heparin has been used empirically in presumed high-risk situations (i.e., visualized thrombus), although there is no base of evidence for such an approach, other than extrapolation from the acute coronary syndrome literature. Bleeding complications are presumably higher with this approach.

Early Revascularization

There is ample evidence supporting the benefit of CEA in patients with stroke and TIA due to carotid bifurcation stenosis [117]. The aim of this intervention is to prevent recurrent ischemic events, which tend to occur early after the index event. In a meta-analysis of three studies of CEA versus medical management, data on 5893 patients demonstrated that benefit from surgery was the greatest in patients randomized within 2 weeks of their index event (Fig. 10.7) [55]. In patients with symptomatic $\geq 50\%$ stenosis, the number needed to treat (NNT) to prevent one stroke at 5 years is 5 if surgery is performed within 2 weeks of the event but 125 for patients with CEA performed after 12 weeks [55, 118]. Patients deriving the greatest benefit from CEA are men, those aged ≥ 75 years, and those who have had a hemispheric stroke as opposed to a TIA or retinal event [55]. The benefit is very robust for TIA patients with $\geq 70\%$ stenosis, but less so for TIA patients with 50–69% stenosis. The risk of stroke and death if CEA is performed within the first days after a cerebral ischemic event is relatively low, provided the patient has stable (i.e., nonprogressive) deficits [119].

Therefore, patients with TIA and minor stroke due to carotid disease with $\geq 50\%$ stenosis should be referred for urgent CEA by an experienced surgeon within the first few days (<2 weeks) of becoming stable. Pretreatment of these patients with ASA is essential to decrease the risk of perioperative stroke [120]. Combined ASA and clopidogrel in the preoperative period is not associated with increased significant bleeding and may provide additional benefit [121]. A meta-analysis found no evidence to demonstrate that carotid artery stenting (CAS) is more beneficial than CEA for stroke prevention, and all stenting studies published since have not meaningfully altered this conclusion [122].

Thrombolysis

While up to 43% of patients with mild or resolving deficits are not offered thrombolysis primarily due to concerns regarding symptomatic hemorrhage, almost a third of these patients will die or be dependent at hospital discharge [2, 3].

A post hoc analysis of the original NINDS t-PA study examined a subgroup of patients deemed to have mild strokes [123]. Among patients with NIHSS <9 (IQR 5–8), patients treated with IV tissue plasminogen activator (rt-PA) had a more favorable outcome at 90 days (OR 2.0, 95% CI 1.5–2.8) and showed a trend toward less deterioration at 24 h but also had a 3% rate of symptomatic ICH (vs. 0% for placebo). However, another post hoc analysis restricted to patients with baseline NIHSS 0–5 found no significant benefit for thrombolysis in this group with mild symptoms [124]. Similarly, a subgroup analysis from the IST-3 trial, which sought

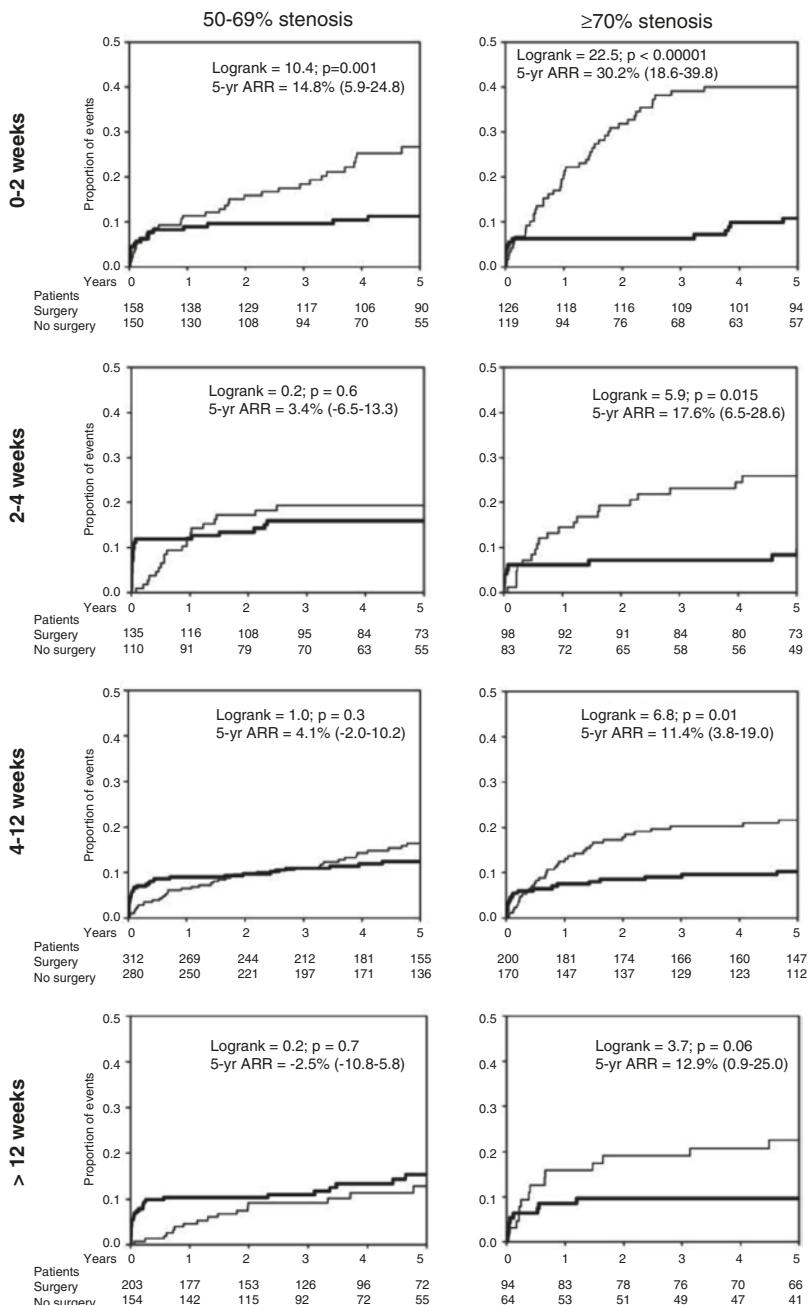


Fig. 10.7 Kaplan-Meier curves showing the effect of CEA on the risk of ipsilateral ischemic stroke and any operative stroke or death in the pooled data from ECST and NASCET in patients with 50–69% stenosis and $\geq 70\%$ stenosis (excluding near-occlusions), stratified according to the time from last symptomatic ischemic event to randomization. The thick line represents patients randomized to CEA and the thin line patients randomized to medical treatment. ARR: absolute risk reduction [90]

to determine whether patients might benefit from rt-PA up to 6 h from stroke, analyzed data for patients with minor strokes (defined as NIHSS ≤ 5). Of the 612 minor stroke patients, 304 were randomized to receive rt-PA. Nine (3%) patients had a symptomatic hemorrhage in the experimental arm compared with none in the control group [125].

A meta-analysis was performed to address the question of rt-PA in minor stroke patients and combined data from 9 randomized acute stroke trials, resulting in a study group of 666 patients presenting with an NIHSS between 0 and 4 [126]. The risk of ICH attributable to thrombolytic therapy seemed to be independent of treatment delay, age, or stroke severity. The use of rt-PA did not result in a significant excess mortality at 90 days (HR 1.11; 95% CI 0.99–1.25; $p = 0.07$), and its benefit was seen in all strokes regardless of their severity, even in patients with NIHSS ≤ 4 . This therapeutic uncertainty has led to the design of the PRISMS trial, a double-blinded, randomized controlled trial evaluating the efficacy and safety of t-TPA vs. ASA patients with symptoms of a minor stroke (NIHSS ≤ 5) within 3 h of onset.

The TEMPO-1 study sought to evaluate the potential role of tenecteplase (TNK-tissue-type plasminogen activator) in patients with acute TIA/minor stroke and CTA evidence of symptomatic intracranial artery occlusion [127]. TNK is a genetically engineered variant of rt-PA with a longer half-life and more fibrin-specific [128], thus potentially resulting in more rapid reperfusion and lower hemorrhage rates [129]. TEMPO-1, a dose escalation study without a placebo group, established both the safety and feasibility of TNK-tPA [127]. The TEMPO-2 trial is currently underway and randomizing patients to TNK versus standard of care (antiplatelet therapy). The primary outcome will examine functional status at 90 days.

It therefore remains unclear if patients with symptoms of minor stroke should be offered thrombolysis, given the substantial risk of symptomatic bleeding that might negate any potential benefit.

Long-Term Secondary Stroke Prevention

As in the EXPRESS and SOS-TIA studies, antiplatelet, antihypertensive, and lipid-lowering therapies should be initiated within 24–48 h of the index event. Choices of antiplatelet agents have been discussed. First-line antihypertensive drugs usually consist of a thiazide diuretic, such as hydrochlorothiazide 12.5–25 mg qd or indapamide 1.25 mg qd with or without an ACE inhibitor like perindopril 4 mg qd depending on whether hypertension is confirmed (target BP $< 140/90$ mmHg). Initial statin therapy includes either atorvastatin or simvastatin (target low-density lipoprotein [LDL] < 2.0 mmol/L). TIA and minor stroke events provide a perfect opportunity to institute long-term secondary prevention at a time when patients are more receptive to starting new medications and adopting lifestyle changes. A more detailed approach to the prevention of secondary stroke will not be discussed here, but as with all stroke patients, the following elements must be addressed: antiplatelet therapy, blood pressure reduction, lowering of lipids with statin agents, glycemic control in patients with impaired glucose tolerance or diabetes, carotid

revascularization or anticoagulation if indicated, smoking cessation, exercise, and counseling on diet and weight loss, as appropriate [93, 94, 130].

Disability Outcomes

Despite the initial mild nature of symptoms in cases of TIA or minor stroke, it is well established that a substantial portion of patients will have a disabling outcome or die. A retrospective analysis of patients not given rt-PA due to mild or improving stroke symptomatology demonstrated that an important proportion of patients died or further deteriorated functionally [131]. The CATCH study enrolled 510 non-disabled patients with minor stroke or TIA and completed a CT/CTA on each within 24 h. About 15% of patients, all of whom presenting with an NIHSS <4, had a disabled outcome defined as mRS of ≥ 2 , some even in the absence of stroke recurrence. Predictors of disability included ongoing symptoms, diabetes mellitus, female sex, and positive findings on CT/CTA [14, 40]. The knowledge that many mild strokes go on to a disabled outcome highlights the opportunity for therapeutic intervention in this population and the need for further research to limit recurrence and disability after TIA.

Conclusions

Definition of Outcome Events: Progression or Recurrence?

The common thinking regarding TIA and minor stroke has been that early risk is assumed primarily by recurrent events. However, there is evidence that up to 90% of early clinical deterioration can actually be attributed to progression of symptoms or infarct growth rather than a true recurrent stroke [33, 50]. This distinction may be important because specific therapeutic interventions might be tailored to attenuate progression of infarcts, while others would aim to minimize the risk of recurrence. Currently, our therapies primarily target the propagation or embolization of thrombus, which might do more to prevent recurrence than to staunch infarct growth. Furthermore, recurrent stroke has often been favored as an outcome rather than functional disability, despite the fact that the latter measure may be more important to patients, their families, and society.

Refining the Role of Neuroimaging

Imaging can further refine clinical risk stratification scores, as the ABCD² + MRI score has demonstrated. Similarly, a clinical score combined with CT/CTA parenchymal and intracranial and extracranial vessel information might be as useful as MRI but more widely and rapidly accessible. More recent work has continued to stress the central role of imaging in the prediction of recurrent vascular events.

Determining Optimal Treatment Regimens

Although EXPRESS and SOS-TIA demonstrated the importance and benefit of early assessment and management of acute TIA, novel and potentially more effective therapies are still lacking. Further high-quality, randomized, controlled trials are needed to investigate the value of different antiplatelet regimens, anticoagulation, blood pressure management, high-dose statins, thrombolysis, endovascular stenting, and neuroprotection in TIA patients at high risk of early deterioration. Moreover, therapies tailored to specific TIA mechanisms are also necessary, particularly for patients with intracranial atherosclerosis and small-vessel infarcts.

The therapeutic paradigm for TIA patients consists of urgent-to-emergent evaluation of high-risk cases, relevant blood work, parenchymal and vascular neuroimaging, cardiac investigations, and a “cocktail” therapeutic approach that takes into account those mechanisms requiring specific treatment.

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Acute Ischaemic Stroke

11

Dheeraj Khurana, Biplab Das, and Rohit Bhatia

Introduction

Stroke is a generic term for a clinical syndrome that includes focal cerebral infarction (ischaemic stroke), focal haemorrhage in the brain and subarachnoid haemorrhage [1]. Effective treatment of the patient who has sustained an acute stroke requires rapid assessment and early intervention. Acute stroke represents a true emergency for which time is crucial and, therefore, evaluation and treatment often proceed simultaneously. Advanced imaging techniques can provide information about the state of brain perfusion, metabolism and the cerebrovascular anatomy to help identify patients with viable brain tissue who may derive the greatest benefit from available therapies. Currently, several agents are available for rapid restoration of perfusion to the ischaemic brain. Development of stroke centres and systems of care have revolutionized the medical management of patients with acute stroke.

Goals of Acute Ischaemic Stroke (AIS) Management

1. To identify stroke with regard to onset time and nature of symptoms and to differentiate between conditions mimicking stroke (Clinical Evaluation)
2. To differentiate AIS from haemorrhage (with unenhanced computed tomography [CT]) and to determine the location, size and vascular territory affected by ischaemic stroke (Neuroimaging)

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3. To determine the patient's eligibility for thrombolytic therapy in ischaemic stroke (Investigations)
4. To prevent and treat complications (Hospital Care)
5. To determine the aetiology and mechanism of stroke (Detailed Evaluation)
6. To initiate secondary stroke prevention (Education)

Clinical Evaluation

The patient's history provides invaluable information for determining the time of symptom onset. Headaches and seizures are infrequent at onset of ischaemic stroke; when present, intracerebral haemorrhage (ICH) or subarachnoid haemorrhage must be ruled out. The initial evaluation is aimed at identifying the main features of ischaemic stroke, to differentiate between conditions mimicking stroke and early recognition of life-threatening complications. The sudden onset of neurological dysfunction is frequently the result of stroke, although other processes can manifest in similar ways.

The National Institutes of Health Stroke Scale (NIHSS) (see Appendix), which is a widely accepted standardized measure of neurological deficits related to AIS [2], can be usually performed in <5 min; the scale can also assist in prognostication. Favourable outcome was seen in 60–70% of patients with scores <10 at 1 year [3, 4], whereas haemorrhagic transformation and worse outcome had a higher incidence in patients with scores of >20 [5].

Initial Investigations

An initial battery of tests should be performed for patients with AIS upon arrival at the emergency department (Table 11.1). These diagnostic tests are mandatory as they establish suitability for thrombolytic therapy as well as exclude metabolic disorders that can mimic stroke symptoms.

Neuroimaging

Brain imaging strategies are important in the patient's initial evaluation. Brain imaging findings, including the size, location and vascular distribution of the infarction, as well as the presence of bleeding, affect both acute and long-term treatment decisions. In addition, information about the possible degree of reversibility of ischaemic injury, status of the intracranial vessels and cerebral haemodynamic status can be obtained from imaging studies [6]. Neuroimaging tests might improve selection of patients for thrombolysis by identifying those with regions of salvageable

Table 11.1 Initial investigations in a patient with AIS

All patients
<ul style="list-style-type: none">• Non-contrast brain CT or brain MRI^a• Blood glucose^a• Serum electrolytes/renal function tests• Electrocardiogram (ECG)• Markers of cardiac ischaemia• Complete blood count, including platelet count^a• Prothrombin time/international normalized ratio (INR)^a• Activated partial thromboplastin time^a• Oxygen saturation
Selected patients
<ul style="list-style-type: none">• Hepatic function tests• Pregnancy test• Arterial blood gas tests (if hypoxia is suspected)• Chest radiography (if lung disease is suspected)• Electroencephalogram (EEG) (if seizures are suspected)

^aRequired for thrombolysis, especially if patient is on anticoagulants. Practically, if history is not suggestive of coagulopathy or drugs, proceeding for thrombolysis is justified after sending a sample rather than losing precious time awaiting the report. Rapid INR testing using a commercially available point-of-care device is recommended

brain tissue, a low risk for haemorrhagic transformation, or occlusions of the large arteries that may or may not be amenable to therapy. At present, the usual brain imaging test is a CT scan. The diagnostic yield and clinical utility of other newer neuroimaging procedures must be weighed against the additional time required for acquiring the data, as well as the availability and financial costs of these tests. The consensus is that the performance of these tests should not delay treatment with intravenous recombinant tissue plasminogen activator (rtPA) [7]. Early CT signs of acute cerebral infarction may be detected within 6 h of symptom onset and include the following: blurring of the internal capsule, loss of the insular ribbon, loss of differentiation between the cortical grey and subjacent white matter and swelling of the cortical gyri with sulcal effacement [8, 9].

The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point score to semi-quantify ischaemic changes in the middle cerebral artery (MCA) territory. One point each is given to the caudate, lentiform, internal capsule, insula and M1, M2, M3, M4, M5 and M6 regions of the MCA making a 10-point score (Fig. 11.1); one point is deducted for abnormality in a region. A lower ASPECTS score therefore suggests a larger area of ischaemia. Although not absolute, ASPECTS scores correlate with outcomes and can also be used for decision-making in thrombolysis. It is a more reproducible semi-quantitative measure of ischaemic change than the one-third MCA territory ischaemic rule. As early changes are often subtle, it is

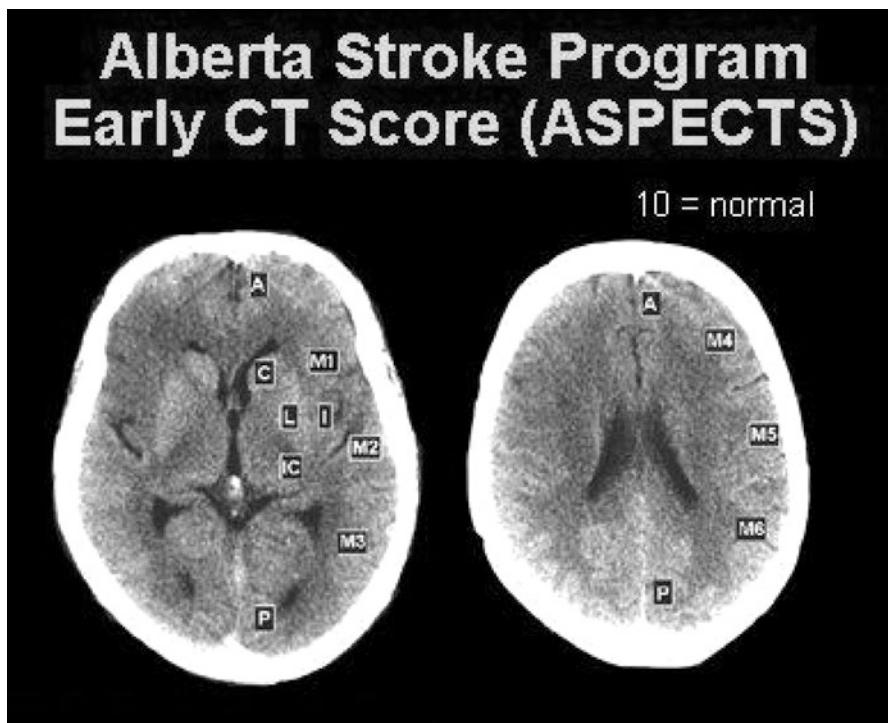


Fig. 11.1 Alberta Stroke Program Early CT Score (ASPECTS) [10 = normal]. *A* anterior circulation, *P* posterior circulation, *C* caudate head, *L* lentiform nucleus, *IC* internal capsule, *I* insular ribbon, *MCA* middle cerebral artery, *M1* anterior MCA cortex, *M2* MCA cortex lateral to insular ribbon, *M3* posterior MCA cortex, *M4*, *M5* and *M6* anterior, lateral and posterior MCA territories, respectively, ~2 cm superior to *M1*, *M2* and *M3*, respectively, rostral to the basal ganglia

important that an experienced reader evaluates the CT. A hyperdense MCA sign (Fig. 11.2) may also be seen, suggesting occlusion of the vessel by a thrombus or embolus [10]. Assessing vascular status (using CT angiogram or MR angiography) in the acute phase of stroke is important for determining the site of occlusion, the status of the major proximal vessels and the collateral status. This helps in making therapeutic decisions, especially when neuro-intervention is being contemplated as an acute recanalization strategy in view of the lower recanalization rates of proximal vessels with i.v. rtPA alone. MRI techniques, such as diffusion (DWI) and perfusion (PWI) mismatch imaging, may help in delineating tissue at risk (penumbra), and hence in selecting patients for reperfusion therapy, especially in the period considered unsafe for thrombolysis. For further details on neuroimaging in stroke, the reader is referred to Chap. 2.

Fig. 11.2 Hyperdense middle cerebral artery (MCA) sign. The hyperdense MCA sign on unenhanced CT of the head (arrow) in patients presenting with presumed acute ischaemic stroke has high specificity and positive predictive value for thromboembolic occlusion of the MCA. It is associated with a poor prognosis



Medical Management of AIS

The main goal of therapy is to restore blood flow and improve perfusion to the affected region of the brain. The cornerstone of this treatment is rapid recanalization of the occluded vessel by removing or dissolving an obstructive blood clot and preventing further clot propagation.

Thrombolytic Therapy

rtPA

In 1996, the US FDA (Food and Drug Administration) approved i.v. rtPA for patients with AIS. rtPA is efficacious and cost-effective for patients with AIS treated within 3 h of symptom onset. The number-needed-to-treat (NNT) one additional patient to achieve minimal or no disability is eight [11]. Earlier administration of i.v. rtPA is associated with better clinical outcomes, underscoring the importance of minimizing the door-to-needle time in the emergency department. The results of the third

European Cooperative Acute Stroke Study (ECASS III) concluded that i.v. rtPA given 3–4.5 h after the onset of stroke symptoms was associated with a modest but significant improvement in clinical outcome and no increased risk of symptomatic intracerebral haemorrhage [12]. The major phase III clinical trials of i.v. thrombolytic agents for AIS have been listed in Table 11.2.

Tenecteplase

Tenecteplase (TNK) is another thrombolytic agent being evaluated for management of acute ischaemic stroke. This lytic drug has an advantage of being more fibrin specific, single bolus dose and a longer duration of action. Previous trials have been evaluated for safety and dose finding ranging from 0.2 to 0.4 mg/kg bolus dose [23, 24].

A recent analysis of the ATTEST [25] and the Australian TNK study [26] suggested better recanalization rates with TNK at 24 h with patients with good recanalization showing a better outcome. However, these trials had significant limitations including open label design, heterogeneity in study design and imaging evaluation. The Study of Tenecteplase Versus Alteplase for Thrombolysis (Clot Dissolving) in acute ischemic stroke ‘NOR-TEST’ has recently been published [27].

1107 ischemic stroke patients were randomly assigned to tenecteplase, 0.4 mg/kg bolus, or alteplase, 0.9 mg/kg infusion within 4.5 h of symptom onset. The drugs were comparable on outcomes using modified Rankin score 0–1 suggesting no difference between two drugs. The rates of intracerebral haemorrhage were similar in two groups. A recent metaanalysis comparing tenecteplase with alteplase included four randomized controlled trials (n=1334) showing significantly better early neurological improvement in tenecteplase group as compared to alteplase group (RR = 1.56, 95% CI [1.00, 2.43], p = 0.05). However, there was no significant difference in functional outcome at 90 days or mortality [28]. Other trials with lower doses are underway to assess better safety and efficacy data. The drug has been recently approved in India, at a dose of 0.2 mg/kg within 3 h of stroke onset. Other thrombolytic agents (e.g. streptokinase, reteplase, desmoteplase) are not currently approved for use in AIS. The guidelines for rtPA use are given in Table 11.3 [29].

Intraarterial Thrombolysis (IAT)

Intraarterial therapy using direct delivery of a lytic agent or using devices to remove a clot is feasible. The potential advantage of intraarterial administration of thrombolytic agents is high concentration, local drug delivery into the clot with reduced systemic effects and increased rates of recanalization.

The use of intraarterial thrombolytics has not been evaluated in large randomized trials, except for the PROlyse in Acute Cerebral Thromboembolism II (PROACT II) trial [30]. In the PROACT II trial, 40% of the r-prourokinase group versus 25% of the control patients had a good outcome (modified Rankin score [mRS] <2). In the r-prourokinase group, the recanalization rate was 66%, while the mortality was 25% versus 27% in the control group. This study suggested the benefit of intraarterial prourokinase in the treatment of MCA occlusions within 6 h of onset. Intraarterial urokinase and rtPA have been beneficial in the treatment of basilar artery occlusions, even beyond 12 h after onset [31, 32]. In an analysis of studies of IAT in patients with AIS, the IAT group showed more favourable outcomes than the control

Table 11.2 Large randomized controlled trials of intravenous thrombolysis for acute ischaemic stroke

Drug	Study	N	Dose	Time from symptom onset (h)	Result	Symptomatic ICH (treatment vs. placebo)
rtPA [13]	NINDS-I	291	0.9 mg/kg	≤3	No improvement in 24-h NIHSS	5.6% vs. 0%
rtPA [13]	NINDS-II	333	0.9 mg/kg	≤3	Better global outcome at 90 days	7.1% vs. 1.2%
rtPA [13]	NINDS-I + II	624	0.9 mg/kg	≤3	Better global outcome at 90 days	6.4% vs. 0.6%
rtPA [14]	ATLANTIS-A	142	0.9 mg/kg	0–6	No benefit	11.3% vs. 0%
rtPA [15]	ATLANTIS-B	613	0.9 mg/kg	3–5	No benefit	6.7% vs. 1.3%
rtPA [15]	ECASS I	620	1.1 mg/kg	≤6	No benefit	19.8% vs. 6.8%
rtPA [16]	ECASS II	800	0.9 mg/kg	≤6	No benefit	8.8% vs. 3.4%
rtPA [17]	ECASS III	821	0.9 mg/kg	3–4.5	Better global outcome at 90 days	2.4% vs. 0.2%
Streptokinase [18]	ASK	340	1.5 mU	≤4	No benefit, excess mortality	13.2% vs. 3%
Streptokinase [19]	MAST-E	310	1.5 mU	≤6	No benefit, excess mortality	21.2% vs. 2.6%
Streptokinase [20]	MAST-I	622	1.5 mU	≤6	No benefit	6.0% vs. 0.6%
Anrcod [21]	STAT	500	0.082–0.167 IU/kg/h × 72 h	≤3	Better outcome at 90 days	5.2% vs. 2.0%
Desmoteplase [22]	DIAS-2	193	57 subjects—90 µg/kg 66 subjects—125 µg/kg	3–9	No benefit	3.5–4.5% vs. 0%

NINDS National Institute of Neurological Disorders and Stroke, *ECASS* European Cooperative Acute Stroke Study, *ATLANTIS* Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; *ASK* Australian Streptokinase Trial, *MAST* Multicentre Acute Stroke Study, *MAST-E* Multicentre Acute Stroke Study Europe, *STAT* Stroke Treatment with Anrcod Trial, *DIAS* Desmoteplase in Acute Stroke

Table 11.3. Guidelines for intravenous use of rtPA in patients with acute ischaemic stroke [29]*Inclusion criteria*

- National Institutes of Health Stroke Scale ≥ 4 (moderate-to-severe deficit)
- Onset time (i.e. when patient was last known to be neurologically normal) ≤ 4.5 h
- No haemorrhage
- Consent of patient and/or next of kin

Exclusion criteria

Thrombolytic therapy cannot be recommended for patients if:

- Current use of oral anticoagulants or prothrombin time >15 s, INR >1.7
- Use of heparin in the previous 48 h
- Platelet count $<100 \times 10^3/\mu\text{l}$ ($100 \times 10^9/\text{L}$)
- Stroke or head injury in the previous 3 months
- Major surgery within the past 14 days
- Pretreatment systolic BP >185 mmHg or diastolic BP >110 mmHg before intracranial haemorrhage (refer to blood pressure management below for lowering BP before thrombolysis)
- Rapid improvement in neurological signs
- Isolated, mild neurological deficits
- Blood glucose <50 mg/dL (or >400 mg/dL)
- Gastrointestinal or urinary bleeding within the past 21 days

Treatment

- rtPA 0.9 mg/kg total or 90 mg maximum (10% as bolus and infusion of the remaining 90% over 60 min)

Follow-up

- Admission to the intensive care unit for 36 h
- Neurological checks with vital signs every 30 min for 6 h, then hourly for 18 h
- Blood pressure and cardiac monitoring
- Avoid placing nasogastric tube, drawing blood, inserting invasive lines or procedures for 24 h, if possible
- No i.v. administration of heparin or antiplatelet drugs during the infusion or for 24 h after the onset of symptoms

Guidelines for the management of rtPA-associated intracerebral haemorrhage

- With clinical suspicion (worsening of NIHSS score or alteration in consciousness) of intracranial haemorrhage, discontinue rtPA infusion
- Urgent CT scan for any neurological deterioration
- Start laboratory tests: prothrombin time, partial thromboplastin time, platelet count, fibrinogen level, blood grouping and cross-matching
- Prepare for administration of 8 units of cryoprecipitated fibrinogen and factor VIII. Prepare for administration of 6–8 units of platelets

group (41.5% vs. 23%, $p = 0.002$), with a lower mortality rate for IAT (27.2% vs. 40%, $p = 0.004$). Symptomatic ICH was more frequent in the IAT group compared with the control group (9.5% vs. 3%, $p = 0.046$) [33]. However, no large clinical trials are available to establish the safety of any other thrombolytic agent in ischaemic stroke. The feasibility of combining intravenous and intraarterial rtPA in treating ischaemic stroke was examined in the Emergency Management of Stroke (EMS) Bridging Trial [34]. The study suggested that this strategy, which included early low-dose intravenous administration of rtPA followed by intraarterial administration of rtPA, could achieve better rates of recanalization and might be

associated with a reasonable degree of safety [34]. In comprehensive stroke centres, with the availability of a neurointerventional radiology team, a bridging therapy with rapid delivery of i.v. rtPA (generally 0.6 mg/kg, although data with a full dose of 0.9 mg/kg is also available) followed by intraarterial thrombolysis using pharmacological/mechanical therapy for major proximal vessel occlusions (MCA M1, M2; internal carotid artery; basilar artery) is carried out with the aim of achieving higher rates of recanalization and a possibly better outcome [35, 36]. However, the recent guidelines of AHA (American Heart Association) [37, 38] suggest that mechanical thrombectomy with stent retrievers is recommended over intra-arterial thrombolysis as first-line therapy (Class I, Level of evidence C) due to the following concerns: intraarterial thrombolysis data is derived from older trials that do not reflect current practice, use of older fibrinolytic agents that are not available, clear dose of intraarterial alteplase is unknown and intraarterial alteplase is not approved by FDA. They also recommended such treatment to be done in an experienced stroke centre, with qualified interventionists (Class I, Level of Evidence 3).

Mechanical Thrombectomy

Mechanical thrombectomy is useful in patients who have contraindications to thrombolytic therapy or have failed recanalization after thrombolysis.

Previously, only two FDA-approved devices for catheter-based mechanical embolectomy—MERCI (Fig. 11.3) and PENUMBRA (Fig. 11.4)—were used based on published studies [39–41]. The Penumbra System (PS; Penumbra, Alameda, Calif) is an embolectomy device specifically designed to remove the thrombus in acute ischemic stroke secondary to large vessel thromboembolism. The device removes the thrombus through two mechanisms: aspiration and extraction.

Recent times have seen increasing use of *stent retrievers* (Fig. 11.5) as the modalities of choice for most stroke intervention procedures. Stent retrievers are self-expandable, re-sheathable and re-constrainable stent-like thrombectomy devices which combine the advantages of intracranial stent deployment with immediate reperfusion and subsequent retrieval with definitive clot removal from the occluded artery [42]. Mechanical thrombectomy by means of stent retrievers is a

Fig. 11.3 The MERCI retriever device

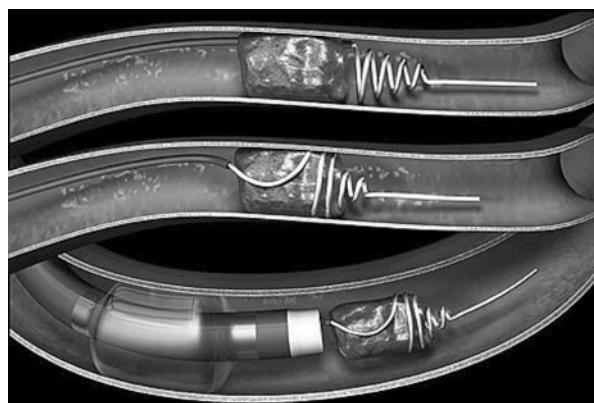


Fig. 11.4 The PENUMBRA system

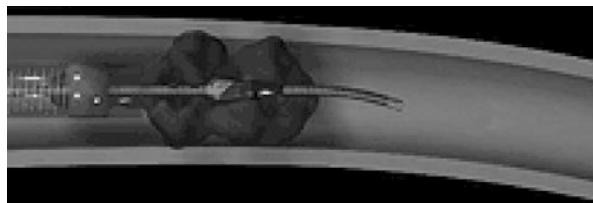


Fig. 11.5 Stent retriever



promising treatment approach for AIS [43]. The entire removal of the device circumvents the most important drawbacks linked with permanent stent implantation. The initial dedicated collective flow restoration and thrombectomy device for acute stroke management was the Solitaire FR (Covidien/ev3, Irvine, USA), receiving the CE mark in 2009 and FDA endorsement in 2012.

Recent times have seen a deluge of major stroke intervention randomized trials and have established bridging therapy with intravenous thrombolysis and endovascular thrombectomy as a standard of care for acute stroke due to major proximal vessel occlusions. Bridging approach has not only led to better recanalization rates but also improved functional outcomes [44, 45]. The details of published trials including MR CLEAN [46], ESCAPE [47], EXTEND-IA [48], SWIFT PRIME [49], REVASCAT [50], THERAPY [51] and THRACE [52] are given in Table 11.4.

In the THERAPY trial, patients with acute ischemic stroke receiving thrombectomy using the Penumbra aspiration system showed a strong trend toward better outcomes than those receiving thrombolysis alone in the THERAPY trial [51]. The trial was stopped early after only 108 of the planned 692 patients had been enrolled because of favourable data on endovascular treatment from other recently reported trials, so the results were not statistically significant. The trial stood out for its novelty in selecting subjects with a clot length >8 mm and to have used Penumbra device to aspirate the same as a part of management. The THRACE trial [52] enrolled 414 patients from 26 centres in France. They were randomly assigned during tissue plasminogen activator (tPA) perfusion if there was no or only minor neurologic improvement (NIHSS<5). The primary endpoint—Independent functional status at 3 months (modified Rankin Scale [mRS] score, 0 to 2)—was achieved in more patients in the interventional group, with an absolute difference of 12.1% that was statistically significant ($P = 0.016$). THRACE trial concluded that mechanical thrombectomy after thrombolysis was superior to thrombolysis alone when initiated within 5 h of stroke onset in patients

Table 11.4 Recently concluded major randomized trials of combination therapy (endovascular intervention and intravenous tPA) in acute ischaemic stroke

Study	Period	Window period	Treatment group			Control group	Major clinical outcome	Functional independence ^b	(% absolute diff. in 2 arms)
			Intervention + IV tPA ^a	Endovascular procedure	IV tPA				
MR CLEAN [46]	2010–2014	6 h	233	Retrievable stent/ mechanical thrombectomy + IA/IA alone	203 (87.1%)	267	242 (90.6%)		13.5
ESCAPE [47]	2013–2014	12 h	165	Retrievable stent	120 (72.7%)	150	118 (78.7%)	Functional independence	23.7
EXTEND-IA [48]	2012–2014	6 h	35	Solitaire stent	35 (100%)	35	35 (100%)	Mortality reduction Early neurological improvement ^c	8.6
SWIFT PRIME [49]	2012–2014	6 h	98	Solitaire stent	98 (100%)	98	98 (100%)	Functional independence	43
REVASCAT [50]	2012–2014	8 h	103	Solitaire stent	70 (68%)	103	80 (77.7%)	Functional independence	31
THRACE, 2016 [52]	2010–2015	<5h	204	Penumbra device	204	208	208	Dramatic neurological improvement ^d	25
THERAPY, 2016 [51]	2012–2014	<4h	55	Stent retriever	53	53	53	Functional independence	15.5
									39

^aIntravenous tissue plasminogen activator^bModified Rankin Score (mRS) ≤2^cReduction of NIHSS by ≥8 points or absolute NIHSS ≤1 on 3rd day
^dNIHSS reduction by at least 8 points or absolute NIHSS 0–2 at 24 h

with moderate 2 to severe stroke due to large artery occlusion. Campbell and colleagues recently published a randomized controlled trial, EXTEND IA-TNK, which compared the efficacy of tenecteplase versus alteplase in achieving reperfusion within 4.5 hours of symptom onset in patients undergoing mechanical thrombectomy. The trial enrolled 202 patients (101 in each arm) and the primary outcome to achieve >50% recanalization or non-visualisation of thrombus was achieved in 22% versus 11% in TNK and t-pa groups respectively ($p=0.03$). Better functional outcome at 90days was significantly better in TNK group as compared to t-pa group ($p=0.04$) [53].

Although most recent bridging trials were carried out on a 6 h window period, the recently concluded *DAWN trial* has suggested further extension of the time window by assessing late-window and wake-up stroke patients. The investigators reported that treatment with a stent retriever up to 24 h, significantly improved functional independence at 90 days when compared to medical management alone (48.6% versus 13.1%) [54]. Yet another example of an extended window trial is DEFUSE-3 which was multi-centre (38 U.S centres), randomized, open-label trial of thrombectomy in 182 patients (92: endovascular and medical therapy, 99: medical therapy alone) 6 to 16 hours after they were last known to be well and who had ischemic tissue that was not yet infarcted as assessed by perfusion imaging. The trial showed statistically significant better functional outcome and lesser mortality ($p=0.05$).in combined therapy group ($p <0.01$) [55].

Intravenous (IV) tissue-type plasminogen activator (tPA) has been the standard of care for treatment of acute stroke [56]. While tPA improves survival and functional outcome, provided it is administered within the window period of 4.5 h [57], its narrow window period, contraindications of recent surgery, head injury, coagulopathy or conditions associated with increased risk of bleeding limits its usage [58, 59]. These contribute to the reduced eligibility of IV tPA (as low as 10%) in all ischemic stroke patients [60]. In addition, prolonged recanalization times, poor revascularization in proximal large artery occlusion and poor outcomes have led to development of other treatment modalities like endovascular approaches [61, 62]. Endovascular thrombectomy is associated with faster and more efficient recanalizations in proximal large occlusion thereby remarkably improved outcomes [44, 63].

Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A) [38, 64]:

- (a) Prestroke mRS score 0 to 1.
- (b) Acute ischemic stroke receiving intravenous rtPA within 4.5 h of onset according to guidelines from professional medical societies.
- (c) Causative occlusion of the internal carotid artery or proximal MCA (M1).
- (d) Age \geq 18 years.
- (e) NIHSS score of \geq 6.
- (f) ASPECTS of \geq 6.
- (g) Treatment can be initiated (groin puncture) within 6 h of symptom onset.

Current evidence supports this approach of combination therapy of intravenous tPA and mechanical thrombectomy [38, 65, 66]. This bridging approach has been associated with higher recanalization rates as well as better outcomes as compared to IV tPA alone. Early initiation of intravenous tPA reduces clot burden with restoration of critical blood flow which facilitates subsequent recanalization by mechanical thrombectomy

[54]. Patients who are not eligible for intravenous tPA prior to endovascular procedure have relatively poor outcome compared to patients who received combination therapy. Prior angiographic localization of clot is important as catheterization of patients without a proximal occlusive clot is unlikely to benefit from interventional procedure.

A high degree of variability exists depending on type of endovascular device being used. A number of different but related endovascular interventions include clot dissolution using intraarterial local delivery of tPA or arterial recanalization by clot disruption, aspiration or retrieval using a mechanical devices. Recent trials have used stent retrievers which are associated with better outcomes compared to other devices, although difference between the exact device types (e.g. Solitaire Flow Restoration device vs. Trevo retriever) needs more evidence.

An individual patient data meta-analysis by the HERMES collaboration [67] ($n = 1287$, 634 assigned to endovascular thrombectomy, 653 assigned to control) from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND-IA) done between December 2010 and December 2014 was recently published. Endovascular thrombectomy was reported to have significantly reduced disability at 90 days compared with control (adjusted OR 2.49, 95% CI 1.76–3.53; $p < 0.0001$). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6. Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations. The meta-analysis underscores the benefit of endovascular thrombectomy in occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location.

Although there is robust evidence of better functional outcome with combination therapy, some factors like effect of general anaesthesia versus conscious sedation, tandem lesions, use of emergent carotid stenting following thrombectomy, etc. are still debatable. Moreover, there is still a lack of skills in terms of endovascular neuro-interventionists especially in developing countries where patients need to be transferred to a tertiary centre having neuro-intervention facilities. The maximal window period for endovascular procedure needs to be deciphered as for intravenous tPA having an evidence-based window period of <4.5 h. Other factors like age (>80 years), low ASPECT or NIHSS score need further evaluation to guide for appropriate treatment modality.

Thrombolysis in Special Situations

Special situations that fall beyond the purview of the published indications of thrombolysis may call for individual decisions on the basis of inferences derived from an understanding of the vascular physiology or sheer clinical experience. Recent guidelines of the American Heart Association [38], have reviewed the benefits and risks of thrombolysis in common clinical situations like age, severity, recent surgery, previous stroke, antiplatelet use, pregnancy etc. Experience suggests that most subjects, who otherwise have a poor predicted outcome without treatment, might benefit from alteplase. In patients with prior stroke and recent surgery, thrombolysis may be beneficial. In conditions such as cervical artery dissection, seizure at onset, pregnancy and during menstruation, stroke in children and individuals 80 years or older of age, patients with recent myocardial infarction (MI), cardiac embolus, asymptomatic intracranial aneurysm, or arteriovenous malformation, thrombolysis can be carried out weighing the risks and benefits [38, 68, 69]. Although patients with minor strokes and those with improving stroke symptoms

are generally excluded from thrombolysis, data suggest that it may not be the correct approach and they might be considered for thrombolysis [38, 70].

Antiplatelet Agents

Use of antiplatelet agents in the immediate acute stroke period has not been well studied. However, oral medications inhibiting platelet function are widely used for secondary stroke prevention on the basis of proven efficacy in numerous large-scale controlled trials. In a recent meta-analysis of 12 trials (94% of data obtained from the International Stroke Trial [IST] and Chinese Acute Stroke Trial), antiplatelet therapy was associated with a significant reduction in death or dependence (OR 0.95, 95% CI 0.91–0.99; $p = 0.008$) and recurrent ischaemic strokes (OR 0.77, 95% CI 0.68–0.86; $p < 0.00001$) [71]. As per the analysis, for every 1000 patients treated with aspirin, 13 avoided death or dependency (NNT 79), and 7 avoided recurrent ischaemic stroke (NNT 140). The use of ticlopidine, clopidogrel or dipyridamole in the setting of AIS has not been evaluated [72].

Initiation of treatment with clopidogrel in a daily dose of 75 mg does not produce maximal platelet inhibition for up to 5 days [73]. A bolus dose of 300 mg clopidogrel inhibits platelet aggregation rapidly [74]. The administration of anticoagulants or antiplatelet agents is currently contraindicated during the first 24 h after treatment with i.v. rtPA. This contraindication is based on the regimen used in the National Institute of Neurological Disorders and Stroke (NINDS) trials [13]. No conclusive data are available for combination antiplatelet agents in AIS. It is, however, a good practice to initiate antiplatelet therapy as soon as possible following an AIS (if thrombolysis is not a consideration).

Antithrombotic Therapy in Acute Stroke

The IST is the only large controlled study using subcutaneous heparin in two doses (5000 U and 12,500 U b.i.d.) for acute stroke, and it found no net benefit over placebo in stroke outcome [75]. The prevention of deep vein thrombosis (DVT) was the primary benefit of taking heparin [75, 76]. The PREVAIL (Prevention of VTE [venous thromboembolism] after Acute Ischemic Stroke with LMWH Enoxaparin) study showed the safety and efficacy of low-molecular-weight heparin (LMWH) in prevention of DVT when used in the early post-stroke period [77].

Interventions in AIS

Surgical Intervention

Carotid Endarterectomy

Indications for immediate carotid endarterectomy (CEA) in a patient with an acute ipsilateral ischaemic stroke are not well established [38]. An intraluminal thrombus



Fig. 11.6 B-mode carotid Doppler (longitudinal) showing a mobile plaque in the proximal left ICA moving in sequence during systole

(Fig. 11.6) associated with an atherosclerotic plaque at the carotid bifurcation may be an indication for emergent CEA.

Endovascular Interventions

Angioplasty and Stenting

Angioplasty and stenting have been used to treat patients with acute stroke secondary to carotid artery dissection [78]. Case series have reported the beneficial effects of angioplasty and stenting in the emergency treatment of intracranial or extracranial carotid and vertebrobasilar lesions in patients with AIS [79–83]. Further studies are required for proper selection of patients and the timing of such a procedure.

Mechanical Devices

These have been discussed above in the section on intraarterial thrombolysis.

Emerging AIS Therapies

Newer therapies targeted at early recanalization have focused on interventional techniques, ultrasound-enhanced systemic drug treatment or combined systemic and endovascular approaches. Bridging therapies, such as neuroprotective strategies, theoretically improve neuronal survival by maintaining tissue salvageability during the additional time required for recanalization approaches. Induced hypothermia appears to be one of the most promising neuroprotective therapies so far. The following methods require further randomized trials to prove their efficacy: induced hypertension, combined intraarterial and intravenous thrombolysis, augmentation procedures, intravenous thrombolysis combined with ultrasound therapies, mechanical clot disruption, and thrombolysis beyond conventional time windows.

Supportive Care for Stroke Patients

The following points should be considered for patient care in a stroke unit. Criteria for admission to the intensive care unit after AIS are given in Box 11.1.

Box 11.1: Criteria for Admission to the ICU After AIS

- Need to monitor for neurological deterioration
- Thrombolytic therapy
- Large hemispheric infarction
- Cerebellar infarction
- Brain stem stroke referable to basilar artery territory
- Fluctuating neurological deficits
- Need for airway management
- Need for intensive cardiovascular monitoring
- Uncontrolled hypertension
- Myocardial ischaemia or congestive heart failure
- In-hospital strokes after medical and surgical procedures

Airway, Ventilatory Support and Supplemental Oxygen

Supplemental oxygen is recommended for patients with hypoxaemia. Routine use of supplemental O₂ in patients with normal arterial oxygen saturation has not been shown to be beneficial [84]. Airway support and ventilatory assistance is recommended for patients with reduced consciousness or a compromised airway.

Elective intubation should be considered in cases of elevated ICP and brain oedema [85]. Patients with stroke who require intubation have a poor prognosis with up to 50% mortality at 30 days [84–88].

Hydration

Elderly patients are more prone to disturbances in water balance. Dehydration leading to a rise in haematocrit and reduction in blood pressure can worsen the ischaemic process. However, haemodilution is not clearly beneficial and requires further study.

Temperature

Fever is associated with increased morbidity, mortality and an unfavourable outcome [85]. Increased neurotransmitter release, enhanced free radical production, and increased metabolic demand may contribute to the damage [88–90]. The source of fever should be sought and adequately treated.

Blood Glucose

Hypoglycaemia may mimic the symptoms of AIS with focal neurological signs, whereas hyperglycaemia is associated with an unfavourable outcome [91, 92].

Thus, prompt measurement and rapid normalization of the serum glucose is an important step. Hyperglycaemic patients have a higher regional lactic acid production, which is associated with decreased survival of penumbral tissue and increased blood–brain barrier permeability [93]. Furthermore, in several thrombolysis trials, hyperglycaemia was found to be associated with haemorrhagic events, a finding that was reconfirmed in a reanalysis of the NINDS rtPA stroke study [92].

Blood Pressure

Persistent arterial hypotension is rare among patients with AIS, but it is associated with an increased likelihood of an unfavourable outcome [94].

Most likely causes for persistent arterial hypotension include cardiac arrhythmias, MI, aortic dissection, volume depletion and gastrointestinal bleeding. Inadequate cerebral perfusion pressure places the ischaemic penumbra at risk for conversion to infarction. The management of hypertension is summarized in Tables 11.5 and 11.6 [29].

Table 11.5 Blood pressure management in patients not undergoing thrombolysis

Blood pressure	Treatment
Systolic \leq 220 mmHg or diastolic \leq 120 mmHg or MAP $<$ 130 mmHg	Treatment is deferred unless required to manage cardiac complications
Systolic \geq 220 mmHg or diastolic \geq 121–140 mmHg or MAP $>$ 130 mmHg	Labetalol 10–20 mg i.v. push (may be repeated or doubled every 20 min up to 150 mg)
Diastolic \geq 140 mmHg	Infuse sodium nitroprusside (0.5 mg/kg/min) Goal of 10%–20% reduction in diastolic BP

Table 11.6 Blood pressure management for patients on thrombolysis

Blood pressure	Treatment
<i>Pretreatment</i>	
Systolic blood pressure $>$ 185 mmHg or diastolic $>$ 110 mmHg	10–20 mg of labetalol i.v.
<i>During and after treatment</i>	
BP is monitored every 15 min for 2 h, then every 30 min for 6 h, and then every hour for 16 h	
Diastolic $>$ 140 mmHg	Sodium nitroprusside (0.5 mg/kg per minute)
Systolic blood pressure 230 mmHg or diastolic 121–140 mmHg	10 mg labetalol i.v. perfusion. May repeat or double every 10 min to a maximum dose of 150 mg or give an initial labetalol bolus and then start a labetalol drip at 2–8 mg/min. If BP not controlled by labetalol, consider nitroprusside drip
Systolic blood pressure 180–230 mmHg or diastolic 105–120 mmHg	10 mg labetalol i.v. perfusion. Repeat or double every 10 min to a maximum dose of 150 mg or give an initial labetalol bolus and then start a labetalol drip at 2–8 mg/min

Management of Complications

Detailed discussion of the management is beyond the scope of this review. Complications associated with AIS are:

Neurological

- Cerebral oedema and herniation
- Intracerebral haemorrhage
- Seizures
- Hydrocephalus

Medical

- Pneumonia
- DVT
- Pulmonary embolism
- Hyperglycaemia
- Hyponatraemia

Cardiovascular

- Hypertensive crisis
- Hypotension
- Arrhythmias
- MI
- Congestive heart failure

Cerebral Oedema and Herniation

Malignant MCA infarction is a term used to describe complete MCA territory infarction with significant space-occupying effect and herniation of brain tissue [74]. The mechanism of ICP elevation in large ischaemic strokes is cell damage-induced cytotoxic oedema. Although cerebral oedema is a potentially fatal complication of stroke, only ~15% of patients develop oedema sufficient to cause clinical deterioration. Ischaemic cerebral oedema occurs during the first 24–48 h and usually peaks around 3–5 days after an ischaemic stroke. The management of cerebral oedema with tissue shift and preservation of the surviving brain forms a crucial part of acute stroke therapy and can be life-saving. Rapid tissue shift resulting in herniation from a large stroke is more common in younger patients than in elderly patients because younger brains have minimal atrophy and, hence, little space to accommodate the swollen brain. The outcome is fatal in most of these patients, with mortality rates of up to 80% with conventional treatment [95]. Early decompressive hemicraniectomy (≤ 48 h) should be strongly considered in any patient ≤ 60 years of age presenting with malignant hemispheric infarction. Further studies are needed to

establish objective neuroimaging criteria for aggressive intervention and to clarify the role of decompressive surgery in older patients (>60 years old). (Please refer to Chap. 27 on ‘Neurosurgical Interventions in Neurological Emergencies’ for details on hemicraniectomy.)

Conclusion

In recent years, we have witnessed significant advances in the field of stroke, including an understanding of the pathophysiology, improvements in diagnostic techniques and advances in therapeutic approaches. The early hospital management of acute stroke requires an organized team effort but a flexible approach so that patients can be evaluated quickly for their eligibility for thrombolytic therapy, treated for coexisting conditions, and alternative diagnoses ruled out. Future directions in the management of AIS are along three main areas: reperfusion (thrombolysis and manipulation of the systemic circulation to augment cerebral blood flow), neuroprotection and investigation of combination therapy with neuroprotectants and thrombolytics.

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Intracerebral Haemorrhage

12

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and Dar Dowlatshahi

Introduction

Stroke is a leading cause of death and disability worldwide. Spontaneous or non-traumatic intracerebral haemorrhage (ICH) is the commonest of all haemorrhagic strokes [1]. It represents the second most common cause of stroke, with an incidence of 8–15% in Australia, the UK and the USA and 25% in Japan [2]. An overall high incidence of ICH is reported in Asians compared with the Caucasian population [3]. Although ICH occurs less frequently than ischaemic stroke, mortality rates are higher—50% for ICH versus 20% for ischaemic strokes. Depending on the aetiology, ICH can be classified as primary or secondary. Primary ICH, which occurs more frequently (78–88%), is caused by the rupture of a vessel usually degenerated by mechanisms such as hypertension [4] or an underlying amyloid angiopathy. Secondary ICH occurs from other disorders that predispose to bleeding. Predilection sites for ICH include the basal ganglia (40–50%), lobar regions (20–50%), thalamus (10–15%), pons (5–12%), cerebellum (5–10%) and

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other brain stem sites (1–5%). Intraventricular haemorrhage occurs in approximately one-third of cases of ICH from extension of bleeding into the ventricular space and carries a worse prognosis. The 30-day mortality in ICH is high (35–52%) and is associated with a high morbidity, as only 10% of the patients are independent at 30 days and 20% at 6 months.

Epidemiology

The incidence of ICH is estimated to be 15–16 cases per 1,00,000 population and is influenced by age, gender, country and race. It is more frequent in males than in females in a ratio of 7:3. After 35 years of age, the incidence of ICH doubles every decade until the 1980s [5]. The rate of occurrence is highest in Asians, intermediate in the black population and lowest in Caucasians. The excessive risk of ICH in African Americans is largely attributable to hypertension, with a higher incidence in young and middle-aged persons, particularly for the deep cerebral and brain stem locations [6].

ICH is closely related to the prevalence of hypertension. Although a substantial fall in hypertension-associated ICH was observed in the UK, persistent high rates in the older age groups were associated with the use of antithrombotic agents and age-related amyloid angiopathy [7].

Aetiology and Risk Factors (Table 12.1)

Causes of ICH vary with age; hypertension being the main risk factor for ICH in all age groups, genders and races. In patients younger than 40 years, arteriovenous malformation is an important cause. Hypertension is a common cause in middle age. In patients >70 years of age, amyloid angiopathy is an important cause. The relative contribution of hypertension may be greater for deep than for lobar ICH [8]. This risk is especially dependent on the blood pressure (BP) control in those people who are not compliant with antihypertensive medication, are 55 years of age or

Table 12.1 Risk factors for and aetiology of ICH

<ul style="list-style-type: none"> • Hypertension • Vascular malformations • Cavernous angiomas • Aneurysm • Amyloid angiopathy • Coagulation disorders • Use of antithrombotics and anticoagulants • Use of sympathomimetics • Vasculitis • Septic emboli • Moyamoya disease 	<ul style="list-style-type: none"> • Intracranial neoplasm • Trauma • Infection • Eclampsia • Cerebral venous thrombosis • Sickle cell disease • Low LDL cholesterol • Older age • Genetic factors • High alcohol intake
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younger or are smokers [9]. The following risk factors have also been identified for ICH:

- Older age.
- High alcohol intake (increases the risk of ICH by impairing coagulation and directly affecting the integrity of the cerebral vessels) [10].
- Black ethnicity.
- Lower total cholesterol and lower LDL cholesterol (several studies have found an inverse relationship between total and LDL cholesterol and the risk of ICH; the association might be stronger for deep haematomas than for lobar haemorrhages [11]).
- Lower blood triglycerides.
- Genetic factors, such as mutations in genes encoding the subunit of factor XIII (which is involved in the formation of cross-linked fibrin), have been observed [12].
- The deposition of β -amyloid protein in the blood vessels of the cerebral cortex and leptomeninges, which characterizes cerebral amyloid angiopathy, is a risk factor for ICH, particularly in the elderly, and may play a role in the development of lobar ICH even in the presence of conventional risk factors, such as hypertension [13].
- Chronic kidney disease might be associated with haemorrhagic stroke, since the former is associated with hypertension, platelet dysfunction and a propensity to bleeding. Kidney disease is often attributed to small vessel disease and may simply be a marker of cerebrovascular small vessel disease—the major mechanism of hypertensive ICH [14].
- Other less consistent associations include male sex, smoking, low physical activity, body mass index (both high and low) and diabetes.

Location of Bleed and Aetiology of ICH

The aetiology of ICH may be suggested by the location of the bleed (Table 12.2).

1. *High BP*: ICH secondary to high BP (HBP) is generally deep (ganglionic) and often with a single focus. In a meta-analysis of 28 studies, hypertension was found to be 2 times more common in patients with deep ICH than in patients with lobar ICH [14]. These haemorrhages usually occur in the territory of

Table 12.2 Aetiology and usual site of ICH

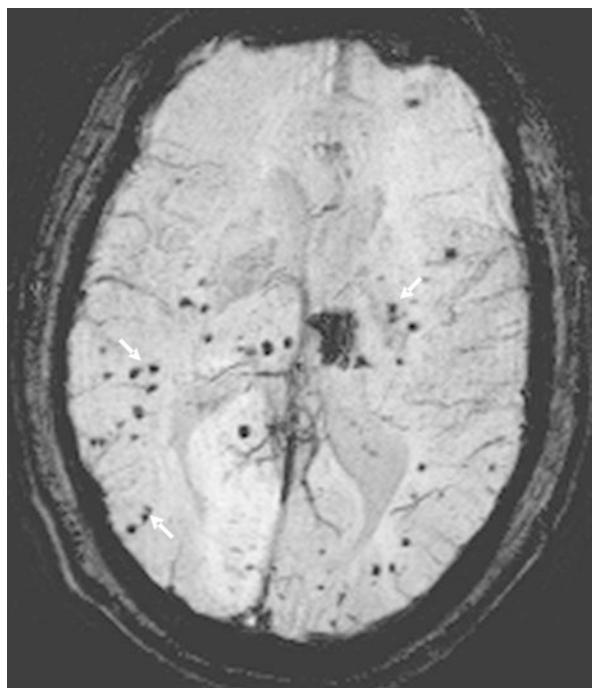
Aetiology	Usual site of bleed
Hypertension	Ganglionic
Amyloid angiopathy	Lobar
Antithrombotic/anticoagulant use	Lobar
Sympathomimetic drugs	Any location
Coagulation disorders	Lobar

penetrating arteries. The wall of the penetrating arteries is damaged by sustained hypertension that causes intimal hyperplasia with hyalinosis. This predisposes to focal necrosis, causing breaks in the wall of the vessels. These ‘pseudoaneurysms’, also called ‘Charcot–Bouchard microaneurysms’ or ‘microatheromatosis’, have been associated with small amounts of blood outside their walls. Massive haemorrhage can occur when the clotting system is unable to compensate for the disruption in the vessel wall [16, 17]. These lesions are also responsible for occlusion of the small vessels that produce lacunar infarcts.

Gradient echo (GRE), susceptibility-weighted imaging (SWI, Fig. 12.1) and T_2 -weighted MRI can detect small regions of focal or multifocal haemosiderin deposition in these patients, which represent remnants of clinically silent cerebral microbleeds [18]. The prevalence of microbleeds has been estimated to be ~5% in healthy adults, 34% in patients with ischaemic stroke and 60% in patients with non-traumatic ICH [19].

2. *Amyloid angiopathy*: This is a degenerative process caused by deposition of the protein β -amyloid in the small arteries and arterioles located in the leptomeningeal vessels and brain cortex. Its incidence increases with age and is uncommon in people younger than 55 years. The bleeds are usually lobar and can be multiple and recurrent.
3. *Coagulation and haemostatic disorders*: The location of ICH is usually lobar, and these disorders occur usually during childhood.

Fig. 12.1 SWI (susceptibility-weighted image) showing multiple small microbleeds (arrows)



4. *Antithrombotic-related ICH:* Antiplatelet drugs increase the likelihood of ICH. The risk of intracerebral bleeding while taking warfarin is 0.5–2% [20]. The volume of the bleed is usually larger, and recurrent bleeding can occur. Leukoaraiosis is a predisposing factor. The risk also increases with age, high BP and previous ischaemic stroke. The location is usually lobar and it carries a poor outcome.
5. *Other drugs:* Bleeds secondary to sympathomimetic drugs can be located anywhere in the brain and can also be associated with high BP.
6. *Cerebral tumours:* These are the cause of ICH in ~6% of patients and are associated with vascular tumours and those with a vasoinvasive capacity.

Mechanisms of Brain Injury in ICH

The main mechanisms of brain injury in ICH are direct mechanical injury to the brain parenchyma by the expanding clot, increased intracranial pressure and herniation secondary to mass effect. Other mechanisms postulated are a decreased blood flow to the area surrounding the clot causing local neuronal ischaemia, which further leads to cytotoxic oedema and the toxic release of excitatory amino acids and inflammatory mediators [20], thrombin-induced activation of the inflammatory cascade and overexpression of matrix metalloproteinases, which contributes to the breakdown of the blood–brain barrier and formation of oedema [21, 22].

Imaging

Computed tomography (CT) scan is the investigation of choice (Fig. 12.2). When a diagnosis other than hypertension is suspected, an MRI scan may be done (Fig. 12.3). CT angiogram (CTA), MR angiogram (MRA) or digital subtraction angiography (DSA) should be ordered when the ICH is suspected to be secondary to an underlying vascular lesion, especially in younger patients in whom an uncommon site of bleeding is present, and in the absence of risk factors, notably hypertension (Fig. 12.4). Since haematoma expansion (Fig. 12.5a, b) is well known in ICH, contrast CT or CTA may be considered to see the presence of the ‘spot sign’ (Fig. 12.6), which may identify patients at risk for expansion (see section below) (Class IIb, Level of evidence B).

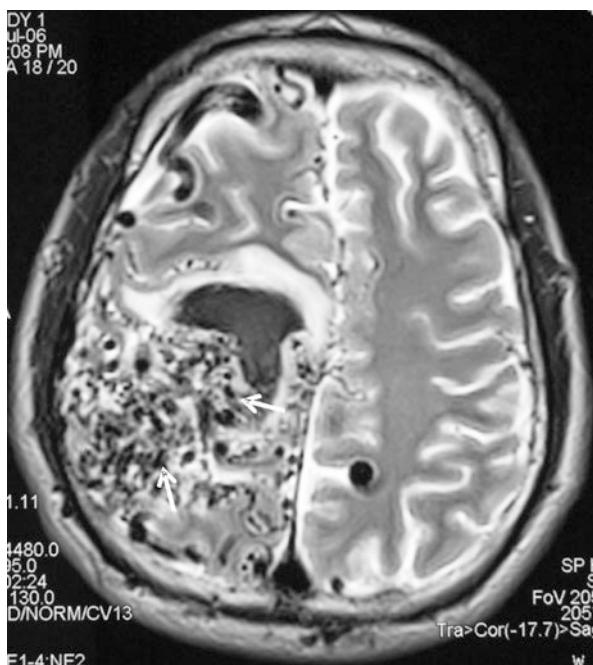
Early Haematoma Expansion

Early haematoma growth (Fig. 12.5a, b) occurs in approximately one-third of patients with ICH and is an independent marker for clinical deterioration and mortality [23, 24]. Haematoma is more likely to expand in the first 6 h after presentation, and, over 24 h, significant haematoma expansion occurs in 38% of patients.

Fig. 12.2 NCCT head showing a large hyperdense area in the right putamen (arrow) suggestive of an acute ICH



Fig. 12.3 MRI head T₂W image showing a large arteriovenous malformation (arrows)



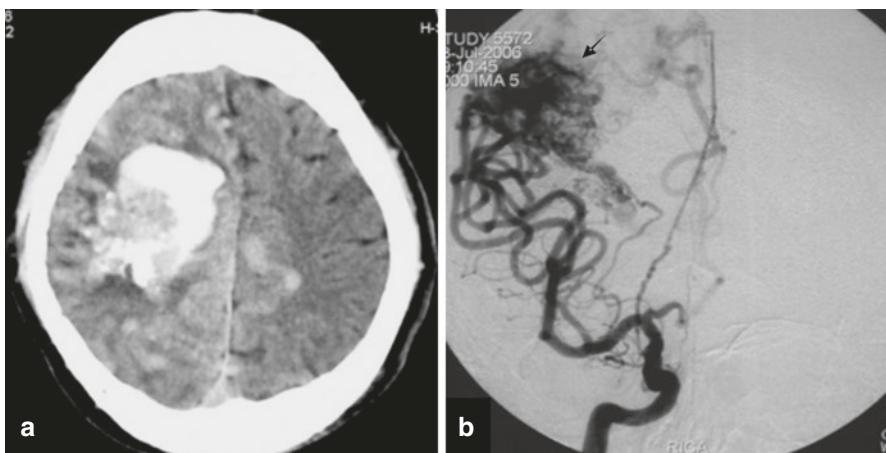


Fig. 12.4 NCCT head (a) shows a large ICH. Digital subtraction angiography (b) shows a large arteriovenous malformation as the cause of the ICH in the same patient (arrow)

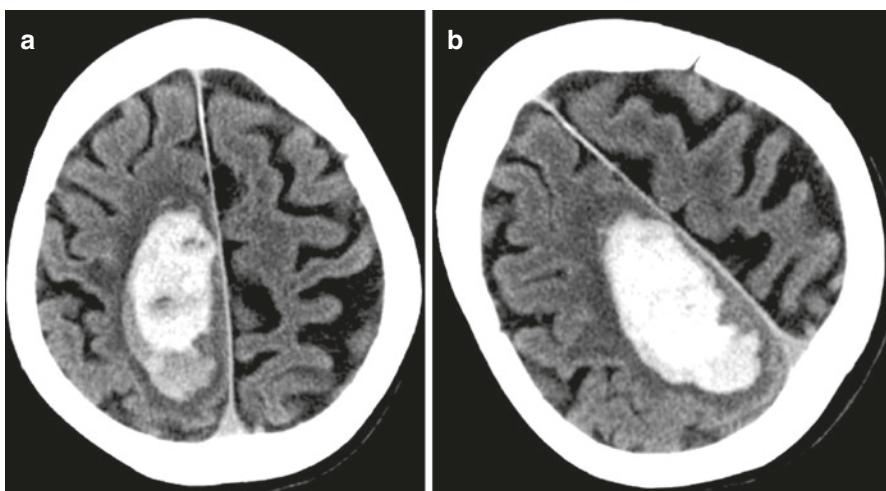


Fig. 12.5 An elderly man with acute-onset headache and altered sensorium. NCCT head (a) done within 3 h of onset reveals an acute lobar haemorrhage (estimated volume 28 cc). CT repeated at 24 h (b) reveals significant increase in the size of the haematoma (estimated volume 42 cc)

The relationship between systemic BP and haematoma enlargement is not clear. Some studies have shown a relationship between elevated systolic BP at the time of hospital admission and haematoma enlargement, whereas others have not.

Several features on baseline neuroimaging can help a clinician predict haematoma expansion: irregular haematoma morphology and heterogeneity [25], baseline haematoma size [26] and, most importantly, contrast extravasation within the

Fig. 12.6 CT angiogram of the head in a patient with acute ICH. ‘spot sign’ (arrow) seen as a dot and linear enhancing area within the haematoma (arrowhead)



haematoma. Early reports suggested that contrast extravasation during MRI, CTA and conventional angiography may represent ongoing haemorrhage [27–31]. In a retrospective case series, contrast extravasation on MRI suggested ongoing bleeding in acute ICH [30]. In a subsequent study, contrast extravasation on CTA was an independent predictor of in-hospital mortality; the fatality rate was 63.5% in patients with extravasation and 16.4% in patients without extravasation [31]. Clinical associations with contrast extravasation included extreme hypertension, decreased level of consciousness and large haematoma volumes.

The first prospective study of CT contrast extravasation included 39 patients presenting with ICH within 3 h of onset of symptom [32]. Haematoma expansion was seen in 77% with contrast extravasation versus 4% without extravasation. Furthermore, patients with contrast extravasation had longer mean hospital stays and a trend towards worse outcomes. A larger retrospective cohort study published the same year showed that CTA contrast extravasation was a strong independent predictor of ICH [33]. The contrast within the haematoma on CTA source images was termed the ‘spot sign’ (Fig. 12.6); radiological criteria were subsequently proposed [34]. Using these criteria, a large multicentre, international prospective CTA study validated the spot sign as a predictor of haematoma expansion and mortality [35]. However, the spot sign’s predictive performance to detect haematoma expansion was modest at best. Nevertheless, these recent developments led to a new generation of haemostatic trials targeting populations at highest risk for haematoma expansion [36].

Clinical Features

Both ICH and ischaemic stroke may have a similar presentation, and it may not be possible to distinguish them without neuroimaging. However, headaches, vomiting and a rapidly deteriorating level of consciousness favour ICH. The onset is sudden, with a focal neurological deficit that can progress quickly in minutes to hours. The intensity of the symptoms rarely fluctuates. Some cases occur during physical activity, coitus or intense emotional activity, although most of them occur during routine activity. ICH can be accompanied by retinal haemorrhages and neck stiffness.

ICH produces both focal and general symptoms. Focal symptoms depend on the location of the haemorrhage and the impairment of surrounding areas by oedema or ventricular involvement. General symptoms depend on the size and mass effect of the haematoma. Those with a large bleed usually have a decreased level of consciousness as a result of increased intracranial pressure and the direct compression or distortion of the thalamic and brain stem reticular activating system [37]. The pressure rise also produces vomiting, especially in ICH located within the brain stem or cerebellum. Headache is more common in lobar and cerebellar ICH because of meningeal and pial vessel distortion. Seizures are also more frequent with ICH in lobar locations. Meningismus can be detected if the blood spreads into the ventricles or into the subarachnoid space.

Neurological deterioration occurs in one-third of non-comatose patients with supratentorial ICH and carries a poor prognosis. A large haematoma volume on CT, rather than clinical predictors, identifies patients at high risk for subsequent worsening [38]. The presence of a large haematoma and ventricular blood increases the risk

Box 12.1: Clinical Features of ICH in Relation to Location¹

Hemispheric ICH

Contralateral hemiparesis, gaze paresis, aphasia (dominant hemisphere, generally left), neglect (right hemispheric), homonymous hemianopia

Thalamic ICH

Contralateral hemiparesis, hemisensory loss, gaze paresis (down and in eyes), miosis, aphasia or confusion

Brain stem

Stupor/coma, hemiparesis, quadriplegia, cranial nerve paresis, crossed hemiparesis (ipsilateral cranial nerve and contralateral weakness), abnormal ocular movements, miosis, hyperpyrexia (pontine), autonomic dysfunction

Cerebellar

Ataxia, gaze paresis, skew deviation, miosis or decreased level of consciousness, hemiparesis, facial weakness

¹ Refer to the text for details. No single feature may be diagnostic. Headache, vomiting and drowsiness may be seen in any location with a sizeable ICH.

of subsequent deterioration and death. Expansion of the haematoma is the most common cause of underlying neurological deterioration within the first few hours after the onset of haemorrhage. Worsening cerebral oedema is also implicated in neurological deterioration that occurs within 24–48 h after the onset of haemorrhage. Infrequently, late deterioration is associated with progression of oedema during the second and third weeks after onset.

ICH Scores and Prognosis

On the basis of clinical and radiological variables, several models have been proposed to predict clinical outcome after ICH. Perhaps the best known ICH score was developed by Hemphill et al. [39] (Table 12.3). Using a combination of haematoma volume, Glasgow Coma Scale (GCS), presence of intraventricular haemorrhage, age and location of bleed, this group derived an ICH scoring system to detect 30-day mortality in a cohort of 152 patients [39]. In this study, no patient with an ICH score of 0 died, whereas all patients with an ICH score of 5 died. Thirty-day mortality rates for patients with ICH scores of 1, 2, 3 and 4 were 13%, 26%, 72% and 97%, respectively. The ICH score was externally validated in 2004 using cohorts of 175 patients [40]. A variant of the ICH score that replaced the GCS with a National Institutes of Health Stroke Scale (NIHSS) score was developed with similar results [41].

In addition to predicting mortality, other scores were developed to assist with prognostication of morbidity [39–42]. Despite the multiple ICH scores, no one score was universally adopted for ICH prognostication. The original ICH score has

Table 12.3 ICH score derivation [38]

Component	ICH score points
Glasgow Coma Scale (GCS) score	
3–4	2
5–12	1
13–15	0
Intracerebral haemorrhage (ICH) volume (cm ³)	
≥30	1
<30	0
Intraventricular haemorrhage (IVH)	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (years)	
≥80	1
<80	0
Total ICH score	0–6

the advantage of external validation, has been used in a variety of published studies and has reliably predicted functional outcome in a recent prospective cohort study [43]. Nevertheless, the ICH score and other prognostic tools can overestimate poor outcomes due to withdrawal-of-care effects.

Following ICH, the most common cause of death reported internationally is withdrawal of care [44]. However, this is not true for India as most patients will continue to get medical support until the complications or the severe nature of the disease itself leads to fatality. As the commonly used prognostic scores do not specifically account for withdrawal of care, they should be used cautiously in an acute setting; therapeutic nihilism in acute ICH based on prognostic models can result in a self-fulfilling prophecy [45]. The most recent validation of the ICH score [43] and the new FUNC (functional outcome risk stratification scale) score for predicting functional independence [46] were developed with this in mind. Nevertheless, given that DNR (do not resuscitate) orders are common in ICH and can result in an overall lack of aggressiveness in care [47, 48], the AHA/ASA Guidelines for the Management of Spontaneous ICH in Adults recommend ‘careful consideration of aggressive full care during the first 24 h after ICH onset’ [49].

Recently, there have been several new predictive scores that specifically incorporate new radiological markers of expansion such as the CTA spot sign. Two studies derived a five-point ‘spot score’ that can predict haematoma expansion, mortality and functional outcome [50, 51]. The spot score uses measurable characteristics of the spot sign in order to refine its predictive performance. In addition, a 9-point predictive rule incorporating both spot sign and other radiological and clinical parameters appears promising as an expansion score [52] as does a similar 24-point prediction rule which does not require a CTA [53]; both rules have similar predictive performances and are currently awaiting external validation. Once validated, clinicians can apply these expansion scores to identify patients at highest risk of deterioration in the acute setting and escalate their level of care.

Medical Management of Primary ICH

The goals of medical management of intracerebral bleed are as follows: (1) emergency medical care, (2) treatment of raised intracranial pressure (ICP) and prevention of brain herniation, (3) reversing the causes of bleeding and preventing haematoma growth and (4) provision of supportive care and prevention of the secondary effects of haematoma.

Emergency Management

As in other medical emergencies, ABC assessment (airway, breathing and circulation) is mandatory. Patients with a reduced level of consciousness, a GCS score <8 and signs of brain stem dysfunction need protection of the airways by means of

intubation. Mechanical ventilation is needed if arterial oxygen saturation cannot be maintained. Monitoring and management of patients with ICH should preferably take place in an intensive care unit because of the acuity of the condition, frequent elevations in ICP and BP, frequent need for intubation and assisted ventilation and multiple complicating medical issues (Class I, Level of evidence 2). Dextrose-containing solutions should be avoided as hyperglycaemia may be detrimental to the injured brain (Class III, Level of evidence 3).

Elevated Intracranial Pressure

ICH perpetuates a vicious circle of elevated ICP and leads to a reduced level of consciousness and hypoventilation. Hypoventilation causes hypoxaemia and hypercarbia which produces vasodilatation and increased ICP which, in turn, leads to a worsening level of consciousness. Monitoring and treating elevated ICP is essential. In patients with severely impaired neurological status (GCS score <9), ICP monitoring, with the aid of either a fibre-optic intraparenchymal monitor or ventriculostomy, may be considered. Treatment is needed when the ICP is >20 mmHg with a goal of cerebral perfusion pressure (CPP) of >60–70 mmHg and a mean arterial pressure of 130 mmHg. Mechanical ventilation parameters should be adjusted to a PCO₂ goal of 30–35 mmHg. Common strategies for managing raised ICP include elevation of the head end of the bed, osmotic therapy, neuromuscular blockade and hyperventilation. Invasive ICP monitoring is generally recommended (Class II A, Level of evidence 2).

Elevation of the head of the bed to 30°, with the head placed in the midline, lowers the ICP by improving the jugular venous outflow. The use of mannitol is controversial and varies between institutions. Many institutions avoid its use altogether. A randomized controlled study showed no benefits with low-dose mannitol in supratentorial ICH [54]. A few non-randomized studies have noted the efficacy of mannitol [55]. Theoretically, hypertonic solutions can enter the parenchyma via the damaged blood–brain barrier and increase oedema due to their increased osmolarity. Mannitol is generally used as a 20% solution at a dose of 1.0–1.5 g/kg given as a rapid infusion intravenously. Randomized controlled trials have shown steroids [56, 57] and glycerol [58] to be ineffective.

Intravenous sedation is needed in unstable patients who are intubated for maintenance of the airway. Intravenous propofol, etomidate or midazolam for sedation and morphine for analgesia and antitussive effect are commonly employed. If the patient is not responsive to analgesia and sedation alone, neuromuscular blockade might be needed. Non-depolarizing neuromuscular blocking agents, such as cisatracurium, rocuronium or vecuronium, are preferred (Class II A, Level of evidence 2). Although hyperventilation is useful in lowering the ICP, this treatment modality is not used in clinical practice, as it simultaneously lowers the cerebral blood flow (CBF). Barbiturates act by lowering the cerebral metabolic activity. They require intensive monitoring and are associated with a significant risk of complications, the most common being hypotension [59].

Reversal of Anticoagulant-Induced Bleed

A history of intake of oral vitamin K anticoagulants (OAC), such as warfarin or coumadin, warrants a PT-INR (prothrombin time–international normalized ratio), which should be obtained at the earliest for the purpose of reversing the anticoagulant effect. It is advantageous to have a point-of-care device as instant INR testing is feasible. Warfarin reversal options include i.v. vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) and recombinant factor VIIa (Table 12.4).

Vitamin K in a dose of 10 mg intravenously is useful in oral anticoagulant-induced bleed, as it leads to sustained reversal of OAC effects but has a delayed onset of action. It should be given promptly to all patients with OAC-induced ICH without delay (Class I, Level of evidence 3) [49].

Being commonly available in hospitals, FFP is frequently used in this setting. FFP needs to be given at a dose of 15–20 mL/kg and therefore requires a large-volume infusion. The disadvantage is the time taken for its preparation, a slower onset of action and tendency for volume overload.

INR can also be reversed with PCC, which is a commercial preparation comprising factors II, IX and X, with or without factor VII. It is slightly cheaper than factor VIIa [60]. The standard dose of PCC is variable, depending on the formula. It corrects INR 4–5 times faster than FFP, generally within 10 min of administration. If the INR continues to remain high, a second dose of PCC is given. The maximum dose varies with the preparation used.

In a recently published INCH trial [61] comparing fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists, the authors observed that four-factor prothrombin complex concentrate (PCC) might be superior to fresh frozen plasma (FFP) in normalizing the INR, and faster INR normalization seemed to be associated with a lesser haematoma expansion with the data showing superiority of PCC over FFP although its clinical benefit yet needs to be shown.

Table 12.4 Drugs used to reverse ICH caused by oral anticoagulants

Agent	Vitamin K	FFP	PCC	rFVIIa
Dose	10 mg i.v.	10–15 mL/kg i.v.	Dose variable depending upon manufacturer 15–50 mL/kg i.v.	40–80 µg/kg i.v.
Comments/concerns	Slower onset of action	<ul style="list-style-type: none"> • Needs cross-matching, thawing • Fluid overload 	<ul style="list-style-type: none"> • Rapid onset of action • May or may not have factor VII depending upon preparation • Thromboembolic complications 	<ul style="list-style-type: none"> • Does not replace all clotting factors • May reverse INR but clotting may not be reversed <i>in vivo</i> • Thromboembolic complications
Level of recommendation	Class IA	Class IC	Class IIA	Class IIIC

FFP fresh frozen plasma, PCC prothrombin complex concentrate, rFVIIa recombinant factor VII

Although there are encouraging reports of the use of factor VIIa in the treatment of anticoagulant-induced ICH either as a primary or an adjunctive therapy, its benefits and risks in this situation need to be studied in a controlled trial [62].

Clinical practice is to withhold therapeutic anticoagulation until at least 1–2 weeks after ICH. Anticoagulation can be initiated safely after 10 days in patients with a mechanical heart valve or atrial fibrillation with a history of cardioembolic stroke [63].

The use of novel oral anticoagulant (NOAC) agents (direct factor Xa inhibitors) is becoming widespread for primary and secondary prevention of stroke among patients with non-valvular atrial fibrillation (AF) and for the prevention of venous thromboembolism [64–66]. According to the clinical trials of the NOACs, 0.2–0.5% of patients with AF receiving one of these drugs may be expected to have an ICH each year [64–68]. In contrast to VKA drugs, the biological effects of NOAC cannot be monitored to date with the standard coagulation assays, and to date, there is not a specific antidote available. Moreover, it still remains unknown whether haematoma expansion occurs in NOAC-related ICH, and clinical experience with haemostatic agents is scarce [69]. Therefore current recommendations are derived from their pharmacological properties and based on expert opinions.

Decision of whether to reverse the action of the NOAC in a patient with an acute ICH remains controversial and should be considered individually, taking into account factors as the severity of the ICH, potential risk of thrombotic events, pharmacokinetics of the NOAC and time from the last dose, renal function, etc. The peak plasma levels of these agents are observed about 2–4 h after ingestion, and their half-lives range from 9–14 h (rivaroxaban) to 14–17 h (dabigatran).

Recent times have seen development of specific antidotes for reversing effects of NOACs. *Idarucizumab*, a humanized monoclonal antibody fragment, binds both free and thrombin-bound dabigatran and has been approved by the Food and Drug Administration (FDA) to reverse the anticoagulant effect of dabigatran [70, 71]. Two separate doses of 2.5 mg each within 15 min of each other (total dose of 5 mg) can be used for emergency life-threatening situation and where other measures have failed. It was seen to be effective in a recent study to completely reverse anticoagulation in over 90% of patients within the first 10–30 min of infusion [71].

Andexanet alfa is a recombinant-modified human factor Xa decoy protein, which reverses the effects of oral factor Xa inhibitors. Two trials, ANNEXA-A (apixaban) and ANNEXA-R (rivaroxaban) [[Clinicaltrials.gov](#) NCT02207725 and NCT02220725], studied the efficacy and safety of andexanet for the reversal of anticoagulation with apixaban or rivaroxaban [71]. The drug was effective in reversing the anticoagulant effect within 2–5 min after administration of the bolus and maintained throughout the continuous infusion. Andexanet alpha was approved by FDA in May 2018 for the reversal of apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding. An ongoing study ANNEXA 4 evaluating its effect on bleeding complications among patients receiving factor Xa inhibitors (NCT02329327) [70] has recently been published. Treatment with andexanet alpha significantly reduced anti-factor Xa activity, and majority (82%) of patients had excellent or good hemostatic efficacy at 12 hours based on prespecified end points [72]. *Aripazine* (PER977) is a small molecule that binds to edoxaban, rivaroxaban, apixaban and dabigatran and is currently undergoing a phase 2 clinical trial [70, 71].

Until specific antidotes are routinely available everywhere, dialysis and activated prothrombin complex concentrate (aPCC) can be used to reverse anticoagulation for patients on dabigatran, while prothrombin complex concentrate (PCC) has shown potential reversing both rivaroxaban and apixaban [73].

If the bleed is secondary to heparin or low-molecular-weight heparin, protamine sulphate is given intravenously (Class I, Level of evidence 2) [74]. Neutralization of heparin occurs within 5 min after i.v. administration. Previous exposure to protamine through the use of protamine-containing insulins may predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug. Patients with a history of allergy to fish may develop hypersensitivity reactions to protamine. Each mg of protamine will neutralize approximately 100 units of heparin. Protamine sulphate should be given by a very slow i.v. injection in doses of not >50 mg of protamine in any 10-min period.

Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; Level of evidence 3). ICH secondary to thrombocytopenia can be treated with a single dose of desmopressin, platelet transfusions or both (Class IIb, Level of evidence 3) [75].

Reversal of Bleed Caused by Thrombolytics

ICH secondary to rtPA (recombinant tissue plasminogen activator) requires immediate suspension of rtPA infusion and assessing the fibrinolytic state with measurement of prothrombin time, partial thromboplastin time and thrombin and fibrinogen levels. Treatment options include FFP, cryoprecipitate and/or platelets. The National Institute of Neurological Disorders and Stroke rtPA study stipulated 6–8 units of cryoprecipitate or FFP and 6–8 units of platelets [76].

Factor VIIa in ICH

Factor VIIa exerts its haemostatic effect by binding to the surface of activated platelets to generate factor Xa. This leads to enhanced thrombin generation and fibrinogen production, which consequently leads to a clot formation. The resultant clot plugs the bleeding arterioles and stops haematoma growth.

Factor VII for Acute haemorrhagic Stroke (FAST) trial showed that factor VIIa had a biological effect but this did not extrapolate to a good neurological outcome [77]. On the basis of these results, routine use of rFVIIa as a haemostatic therapy for all patients with ICH within a 4-h time window cannot be recommended (Class III, Level of evidence 2). A post hoc analysis of the FAST trial showed that a subgroup of patients (age \leq 70 years, symptom onset $<$ 2.5 h, ICH volume $<$ 60 mL, intraventricular bleed $<$ 5 mL) might benefit from factor VIIa [78]. The dose cited in the literature is generally 40–80 µg/kg [66]. Factor VIIa is contraindicated in patients with recent myocardial infarction within the previous 2 weeks, recent ischaemic stroke,

concomitant use of PCC or known hypersensitivity. Its use is associated with the occurrence of thromboembolic events. The major concern in using factor VIIa or PCC is the risk of thromboembolic events. A recent meta-analysis on factor VIIa use showed that although its use reduces the growth of the haematoma, it does not improve patient survival or functional outcome after ICH, with an increased risk of thromboembolic events [79]. A potential application of this drug for ultra-early therapy in patients with a positive ‘spot sign’ remains to be seen, and two trials were carried out in this regard [36] (STOP-IT: Spot Sign for Predicting and Treating ICH Growth Study; www.stopitstudy.org). The trials were stopped due to very slow recruitment. A total of 69 spot-positive patients and 73 spot-negative patients were enrolled. Results of the two studies were pooled for analysis and presented in the international stroke conference 2017. In adjusted analysis, no significant benefit of factor VII, either on the primary outcome, or the secondary outcome was observed. The overall use of this drug in the management of spontaneous ICH remains unclear at present.

Management of BP

It is difficult to determine whether elevated BP is a cause of haemorrhage growth or an effect of increasing volumes of ICH and increased ICP. Guidelines for BP management in ICH provided by the American Heart Association (AHA) Stroke Council suggest acute lowering of BP when the mean arterial pressure (MAP) is 130 mmHg or greater [49, 80]. Modest reductions (15–20%) in BP appear to be safe. Overaggressive treatment of BP may decrease the CPP and theoretically worsen brain injury, particularly in the setting of increased ICP [80].

In patients with small- to medium-sized acute intracerebral bleeds, CBF was preserved with arterial BP reductions by ~15% [81]. The INTERACT (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage) study showed that an early intensive BP-lowering treatment is clinically feasible and well tolerated and seems to reduce haematoma growth in ICH (Table 12.5) [82]. This study provides proof of the concept that early rapid lowering of BP in acute ICH is safe. The INTERACT 2 study showed that the intensive lowering of blood pressure is safe. An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure [83]. Although results did not show a statistically significant reduction in the rate of the primary outcome of death or severe disability, there was a strong trend towards benefit ($p = 0.06$). Another study named the Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH) trial, in which systolic blood pressure is reduced using intravenous nicardipine hydrochloride targeting three tiers of sequentially escalating SBP reduction goals (170–199, 140–169 or 110–139 mmHg), has shown a nonsignificant relationship between magnitude of SBP reduction and haematoma expansion and 3-month outcome [84]. A recently concluded ATACH 2 study [85] randomized 1000 subjects to a systolic blood pressure target of 110–139 mmHg (intensive treatment) or to 179 mmHg (standard treatment) with intravenous nicardipine and failed to show reduction in death or disability with intensive lowering of BP. The primary outcome was death or

Table 12.5 Trials comparing intensive and standard reduction of BP in acute ICH

S. No.	Trial	Number of subjects	Study group randomization	Results
1.	INTERACT 1	404 ICH patients	Randomized into target SBP of 140 mmHg within 1 h or target SBP of 180 mmHg as per standard guidelines	Safe. Trend towards lower haematoma growth. No change on clinical outcome
2.	INTERACT 2	2829 ICH patients	Enrolled within 6 h of onset of event Subjects randomized into intensive lowering (<140 mmHg within 1 h), $n = 1399$ versus guideline (<180 mmHg) BP, $n = 1430$	Safe. No difference between death, disability between the groups on primary end point, although trend presents ($p = 0.06$) in benefit of BP lowering. An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure
3.	ICH-ADAPT	75 ICH patients	Systolic BP > 150 mmHg randomly assigned to antihypertensive treatment protocol targeting a systolic BP of <150 mmHg ($n = 39$) or < 180 mmHg ($n = 36$). Patients underwent CT perfusion imaging 2 h post randomization The primary end point was perihematomal relative CBF	Rapid BP lowering does not reduce perihematomal CBF. Data suggests that acute BP reduction does not precipitate cerebral ischaemia in ICH patients
4.	ATACH	80 ICH patients	4 tier dose escalation with nicardipine	Safe and feasible to lower BP
5.	ATACH 2	1000 ICH patients	500 in each arm. Randomized into systolic blood pressure target of 110–139 mmHg (intensive treatment) or to 179 mmHg (standard treatment) with intravenous nicardipine within 4.5 h of symptom onset Primary outcome was death or disability (mRS 4–6)	Failed to show reduction in death or disability with intensive lowering of BP The rates of adverse events were higher in the intensive group (1.6%) versus standard care (1.2%). Renal adverse event rates within 7 days of randomization were significantly higher in the intensive-treatment group (9.0%) than in the standard-treatment group (4.0%); $P = 0.002$

disability at 3 months after randomization. The primary outcome of death or disability was observed in 38.7% of the participants (186 of 481) in the intensive-treatment group and in 37.7% (181 of 480) in the standard-treatment group (adjusted analysis: relative risk, 1.04; 95% confidence interval, 0.85 to 1.27). The rates of adverse events were higher in the intensive group (1.6%) versus standard care (1.2%). Renal adverse event rates within 7 days of randomization were

significantly higher in the intensive-treatment group (9.0%) than in the standard-treatment group (4.0%); $P = 0.002$.

These studies suggest that acute lowering of SBP to 140 mmHg in patients presenting with SBP in the range 150–220 mmHg is probably safe but too much lowering may lead to more adverse events especially renal. More than 3000 patients were enrolled in seven prospective randomized controlled clinical trials assessing the safety and efficacy of intensive BP reduction which have shown that BP lowering (<140 mmHg systolic) is well tolerated and may improve functional outcomes [86].

In general, the AHA Guidelines [49] (Table 12.6) indicate a modest reduction of BP (e.g. MAP of 110 mmHg or a target BP of 160/90 mmHg) using intermittent or continuous intravenous medications with frequent clinical examinations every 15 min if the SBP is >180 mmHg or MAP is >130 mmHg, and there is no evidence of or suspicion of elevated ICP (Class IIB, Level of evidence 3). In case a high ICP is suspected, it is preferable to lower the BP by monitoring the ICP and maintaining the CPP at ≥ 60 mmHg. In case the SBP is ≥ 200 mmHg or MAP ≥ 150 mmHg, then aggressive lowering of BP with continuous i.v. infusion and BP monitoring every 5 min is suggested [49].

BP reductions can be achieved with parenteral antihypertensive agents, such as labetalol, enalaprilat, esmolol or nicardipine. Nitroprusside is generally not preferred as it can increase the ICP secondary to vasodilatation. The individual agents are detailed in Table 12.7.

Table 12.6 Guidelines for the management of BP in ICH (adapted from AHA guidelines [49])

Blood pressure (BP)	Guidelines
If SBP ≥ 180 mmHg or MAP ≥ 130 mmHg and normal ICP suspected	Modest reduction of BP to MAP 110 mmHg or BP around 160/90 mmHg. Re-examine patient every 15 min
If SBP ≥ 180 mmHg or MAP ≥ 130 mmHg and high ICP suspected	Consider monitoring ICP and accordingly lower BP. Maintain CPP at ≥ 60 mmHg
If SBP ≥ 200 mmHg or MAP ≥ 150 mmHg	Consider aggressive BP reduction with i.v. infusion. Monitor BP every 5 min

Table 12.7 Drugs used to treat hypertension

Drug	Standard dose	Mechanism of action	Cautions
Labetalol	10–20 mg bolus every 10 min, up to 300 mg; 0.5–2 mg/min infusion	α - and β -adrenergic receptor blocker	Bradycardia, congestive heart failure, bronchospasm, hypotension
Enalaprilat	0.625–1.2 mg q 6 hourly i.v.	ACE inhibitor	Precipitous fall in blood pressure with high-renin states, variable response
Nicardipine	5 mg/h, increased by 1–2.5 mg/h q 15 min, up to 15 mg/h	L-type calcium channel blocker	Severe aortic stenosis, myocardial ischaemia, hypotension
Esmolol	500 μ g/kg/min bolus; 50–300 μ g/kg/min	Beta-1 receptor antagonist	Bradycardia, congestive heart failure, bronchospasm

Management of Associated Medical Conditions

Hyperglycaemia

High blood sugar was associated with increased 28-day mortality in both diabetic and nondiabetic patients [87]. Strict glucose control after ICH is recommended (Class IIA, Level of evidence 3).

Fever

Fever is an independent prognostic factor in ICH [88] and should be aggressively treated (Class I, Level of evidence 3). Fever causes increased intracranial hypertension secondary to volume homeostasis [89].

Seizures

A lobar location of ICH has been observed to be significantly associated with the occurrence of early seizures [90] and was independently associated with increased midline shift after intraparenchymal haemorrhage [91]. Continuous EEG may be done for patients where the depressed level of consciousness seems out of proportion to the severity of injury [49]. Initial choice of medication includes benzodiazepines, such as lorazepam or diazepam, followed directly by intravenous fosphenytoin or phenytoin (20 mg/kg) (Class I, Level of evidence 2). An alternative to phenytoin infusion is levetiracetam (500 mg q 12 h, adjusted for renal insufficiency) [92].

The prophylactic use of antiepileptic drugs in ICH has not been substantiated by randomized, controlled trials and is not recommended.

General Care

General measures include swallow assessment, deep vein thrombosis (DVT) prophylaxis, physiotherapy and speech therapy. Nasogastric feeding is initiated in patients with dysphagia. Persistent dysphagia mandates a percutaneous endoscopic gastrostomy (PEG). Dynamic compression stockings are helpful in the prevention of DVT (Class I, Level of evidence 2). In an uncontrolled study, subcutaneous heparin at a dose of 5000 U t.i.d. when started on day 2 after haemorrhage has been shown to reduce significantly the frequency of DVT compared with treatment begun on day 4 or 10, with no concomitant increase in haematoma expansion (Class IIB, Level of evidence 2) [93]. Two small randomized studies found no difference in DVT incidence and no increase in bleeding, in patients given low-dose subcutaneous heparin initiated at day 4 or at day 10 after ICH [93, 94]. Treatment with low-molecular-weight heparin (enoxaparin 40 mg daily) is a reasonable alternative if renal function is normal (Class IIB, Level of evidence 3).

Surgical Management

Please refer to Chapter 27 on ‘Neurosurgical Interventions in Neurological Emergencies’ for details of surgical management.

Conclusion

ICH is a common and important neurological emergency with a high morbidity and mortality. The most common cause is hypertension. Newer data from studies suggests BP lowering to be safe. Haemostatic drug trials using spot sign as a surrogate marker of haematoma expansion are currently ongoing. Surgical therapy should be individualized and performed in a timely manner for deteriorating patients. Newer trials with minimally invasive surgical techniques are underway. Close monitoring and timely treatment of complications is mandatory. Timely recognition and aggressive management of this neurological condition is critical.

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Cerebral Venous Thrombosis

13

Rohit Bhatia, Bhavna Kaul, and Deepa Dash

Introduction

Cerebral venous thrombosis (CVT) was first recognized in the early nineteenth century when Ribes, in 1825, described the clinical and autopsy spectrum of superior sagittal sinus thrombosis in a 45-year-old man suffering from a disseminated malignancy [1]. CVT is an important cause of stroke, with diverse clinical features, predisposing factors, brain imaging findings and outcomes. Many cases may remain clinically undetected in view of the variable clinical signs and a generally good prognosis.

Epidemiology

The global prevalence of CVT is ~5 per million. The condition usually tends to affect younger age groups and is relatively more common in women, particularly in the age group of 20–35 years because of pregnancy, the puerperium and oral contraceptive use [2]. Among 958 young women with stroke from 8 Asian countries, the prevalence of CVT was found to be 21% [3]. This disease appears to be common in the South Asian region. In an autopsy series [4], CVT accounted for 10% of all strokes, and in another published report, it was 17% [5]. The latter study suggested that CVT accounts for half of all strokes in young people [5].

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Aetiology (Table 13.1)

Predisposing factors can be identified in up to 80% of patients [6]. In the pre-antibiotic era, pyogenic infections in the catchment area were the commonest cause of CVT. Although any of the sinuses could be involved, the commonly involved ones were the cavernous sinus, lateral sinus and superior sagittal sinus, in descending order of frequency [7]. With the advent of antibiotics, the incidence of post-infective CVT has reduced markedly, and, in a study published in 1992, infections accounted for only 8% of cases [8].

Among the non-infective causes, the most common are the post-partum state, systemic conditions such as connective tissue diseases, anaemia, granulomatous and inflammatory bowel diseases and malignancies.

In young women, CVT occurs more frequently during the puerperium than during pregnancy. Oral contraceptives and various coagulation disorders have often been implicated. A Dutch study found an age-adjusted odds ratio of 13 for oral contraceptive use and risk of CVT [9]. Hereditary prothrombotic conditions (e.g. factor V Leiden mutation, deficiency of proteins C, S and antithrombin III, as well as prothrombin gene mutations) may account for CVT in one-third to two-thirds of children and in 10–15% of adults [10]. The risk of a carrier of these prothrombotic

Table 13.1 Causes of and risk factors associated with cerebral venous sinus thrombosis

<i>Genetic prothrombotic conditions</i>	<i>Haematological conditions</i>
Antithrombin deficiency	Polycythaemia—primary and secondary
Protein C and protein S deficiency	Thrombocythaemia
Factor V Leiden mutation	Leukaemia
Prothrombin mutation (the substitution of A for G at position 20210)	Anaemia, including paroxysmal nocturnal haemoglobinuria
Homocysteinaemia caused by mutations in the methylene tetrahydrofolate reductase gene	
<i>Acquired prothrombotic states</i>	<i>Drugs</i>
Nephrotic syndrome	Oral contraceptives
Antiphospholipid antibodies	Asparaginase
Homocysteinaemia	
Pregnancy	
Puerperium	
<i>Infections</i>	<i>Mechanical causes, trauma</i>
Otitis, mastoiditis, sinusitis	Head injury
Meningitis	Injury to sinuses or jugular vein, jugular catheterization
Systemic infectious disease	
<i>Inflammatory disease</i>	<i>Neurosurgical procedures</i>
Systemic lupus erythematosus	Lumbar puncture
Wegener granulomatosis	
Sarcoidosis	
Inflammatory bowel disease	
Behçet syndrome	
	<i>Miscellaneous</i>
	Dehydration, especially in children
	Cancer

conditions developing CVT is increased by the coexistence of other factors. It is therefore advisable to discourage women who have a history of venous thrombotic disease from using oral contraceptives, especially if they are carriers of a prothrombotic disorder.

CVT is typically multifactorial. So even if a risk factor or a cause has been identified, this should not deter clinicians from looking for other risk factors. In the ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis), 44% of the patients had more than one cause or predisposing factor; congenital or genetic thrombophilia was found to be present in 22% of patients [11]. In 20–30% of cases of CVT, extensive search revealed no underlying cause, indicating the need for a close follow-up [12]. Closed head injury is an important but often overlooked and underdiagnosed cause of cerebral venous sinus thrombosis. This warrants special mention as the management protocols for CVT in patients of head trauma with skull fractures and contusions are not clearly established. In a retrospective review of 908 patients with skull fractures, 22 patients had a fracture over a sinus and concomitant venogram, as mandated by the inclusion criteria in the study [13]. It was found that 22 (34.9%) patients demonstrated a thrombus in at least 1 sinus. This study demonstrated that over 10% of skull fractures involve venous sinuses. The outcome measured in terms of length of hospital stay was found to be better in paediatric versus adult patients.

A recent review discusses the potential risk factors for CVT and the scientific evidence of association [14].

Pathophysiology

The two main effects of CVT are intracranial hypertension and parenchymal ischaemia. These two aspects often coexist but manifest as distinct clinical symptoms. In case of a limited sinus occlusion, an effective collateral flow through cortical collaterals or within the deep circulation limits parenchymal damage to a localized oedema without ischaemic lesions. If the thrombotic process is more widespread and involves more than one sinus, collateral flow is insufficient to allow venous drainage; the consequence is a dramatic increase in capillary pressure, leading to leakage of fluids in the extracellular compartment, brain swelling and intracranial hypertension. In case a cortical vein gets thrombosed, collateral circulation is negligible, and venous stroke develops rapidly.

Clinical Features

CVT presents with a remarkably wide spectrum of signs and modes of onset, thus mimicking numerous other disorders. The clinical profile is generally determined by the following: (1) underlying sinus/venous system involvement; (2) mode of onset—acute, subacute or chronic; (3) time interval between onset of disease and clinical presentation; and (4) nature of the primary disease giving rise to CVT. CVT

is acute (duration of <2 days) at presentation in 30% of patients, subacute (duration of 2 days to 1 month) in 50% of cases and chronic (duration of >1 month) in 20% of patients. Occasionally, symptoms can progress over 6 months or more. Acute onset, often associated with focal signs, is typical of obstetrical and infectious CVT. Subacute or chronic onset is frequently observed in inflammatory diseases and in coagulation disorders. The chronic pattern of onset is typical of isolated intracranial hypertension. Thrombosis of the different sinuses and veins also results in diverse clinical pictures (Table 13.2).

Headache is the most frequent symptom, occurring in >80% of patients [15]. It is also the most common initial symptom, present in 70–75% of patients before the onset of other neurological manifestations. The headache of CVT has no specific features; it can be of any grade of severity, diffuse or localized, mostly persistent but also intermittent, and sometimes occurring in attacks mimicking migraine. Its duration is usually a few days, but it may arise suddenly and be severe, mimicking subarachnoid haemorrhage. Headache can occur in the absence of any other neurological signs or symptoms, causing great diagnostic difficulties. Papilloedema is present in ~50% of patients with CVT and can be associated with bilateral transient visual obscurations. Seizures occur during the course of CVT in ~40% of patients; they may be partial or generalized. Focal sensory or motor signs occur in 30–80% of patients; alternation from one side of the body to the other is a highly suggestive but late pattern of presentation of sinus thrombosis.

Other manifestations include aphasia, hemianopia, various cognitive disturbances, psychiatric disturbances, cranial nerve palsies and cerebellar signs. Impaired

Table 13.2 Presenting features of dural sinus thrombosis at different sites

Superior sagittal sinus	Presentation can vary but commonly presents with bilateral motor deficit involving the lower limbs, seizures or isolated intracranial hypertension. Extension to the cortical veins of the parietal and Rolandic areas can lead to presentation in the form of acute or progressive motor and sensory deficit, predominantly involving the lower limbs
Cavernous sinus thrombosis	Ocular signs dominate the clinical picture with orbital pain, chemosis, proptosis and oculomotor palsies
Lateral sinus thrombosis	Acute lateral sinus thrombosis may present with headache, vomiting, drowsiness with or without focal motor deficits. Isolated thrombosis of the lateral sinus may also present as isolated intracranial hypertension. Extension to contiguous sinuses leads to other features. If the superior and inferior petrosal sinuses get involved, the patient presents with palsy of cranial nerves V and VI; adjacent cortical vein involvement leads to aphasia, and involvement of the jugular bulb leads to paresis of cranial nerves IX, X and XI
Deep cerebral veins	Occlusion of the deep cerebral venous system is usually associated with a clinical picture of coma, confusion and motor deficits, which are usually bilateral. In patients with parenchymal lesions, the clinical picture is more severe. Patients are more likely to be comatose or to have motor deficits, aphasia and seizures and are less likely to present with isolated headache. Focal or generalized seizures, including status epilepticus, are more common than in other stroke types

mental status is present during the evolution of CVT in almost 50% of cases. It is rarely an initial symptom. Usually moderate in degree, it is secondary to raised intracranial pressure (ICP) and associated with headache and seizures. Severely altered mental status can be a postictal event or a sign of deep venous system thrombosis.

Patterns of Presentation (Table 13.3)

Despite the diverse clinical manifestations and modes of onset, four main clinical patterns of CVT are evident. These include the following:

1. *Focal deficits or partial seizures*: If found in association with headaches, seizures or altered consciousness, extremity weakness or sensory loss, an immediate suspicion of CVT should be aroused. However, CVT may also manifest as isolated seizures or isolated transient focal deficits, mimicking migrainous auras or transient ischaemic attacks. Acute, persistent focal patterns of presentation mimic arterial strokes, while subacute manifestations mimic abscesses or tumours.
2. *Isolated intracranial hypertension*: May present with headache, nausea, vomiting, papilloedema, transient visual obscurations and eventually VI nerve palsy. CVT presenting as isolated intracranial hypertension (ICH) can be mistaken for idiopathic intracranial hypertension (IIH) if appropriate investigations are not performed.
3. *Subacute diffuse encephalopathy*: Characterized by a decreased level of consciousness and sometimes seizures without clearly localizing signs or recognizable features of ICH. Such cases can mimic encephalitis or metabolic disorders.
4. *Painful ophthalmoplegia*: This is observed in patients with cavernous sinus thrombosis and presents as palsy of cranial nerves III, IV or VI, chemosis and proptosis. In some cases, often because of the masking effect of an inadequate antibiotic regimen, cavernous sinus thrombosis can take a more indolent form with isolated VI nerve palsy, mild chemosis and proptosis. Extension to other sinuses and thrombosis of the intracavernous portion of the internal carotid arteries are particularly dreaded.
5. Less common forms of presentation include subarachnoid haemorrhage and acute subdural hematoma [16]. However, vigil is required so as to not miss these underlying aetiologies.

Table 13.3 Patterns of presentation in CVT

Common	Uncommon
Focal syndrome (deficit and/or seizure)	Cavernous sinus syndrome
Diffuse encephalopathy	Subarachnoid haemorrhage
Isolated intracranial hypertension	Thunderclap headache
Any combination of the above	Attacks of migraine with aura
	Isolated headache
	Acute subdural hematoma

Diagnosis

Diagnosis of cerebral venous sinus thrombosis (CVST) is based on a high degree of suspicion in a patient presenting with typical symptoms in a setting conducive to venous sinus thrombosis. Nevertheless, a conclusive diagnosis relies heavily on imaging modalities. Although conventional angiography is the gold standard for diagnosis of venous sinus thrombosis, magnetic resonance venography (MRV) has the advantage of being noninvasive and nearly as sensitive in the diagnosis of CVT. Imaging findings of CVT can be categorized as direct, when there is visualization of cortical or dural sinus thrombus, or indirect, when there are ischaemic changes related to venous outflow disturbance.

Clues that help to differentiate a venous from an arterial infarct are given in Table 13.4. The location of the infarction with respect to the expected course of venous drainage may give a clue to the venous structure involved. Thrombosis of the superior sinus may result in infarction of the parasagittal region (Fig. 13.1b).

Table 13.4 Points of difference between arterial and venous stroke

Points of difference	Arterial stroke (Fig. 13.1a)	Venous stroke (Fig. 13.1b)
Territory	Corresponds to a particular arterial territory	Does not correspond to any arterial territory
Mass effect	Proportionate to infarct size	Disproportionate to infarct size
Haemorrhagic transformation	Uncommon	Common
Pattern of involvement	Subcortical involvement, sparing of cortex	Cortical and subcortical involvement

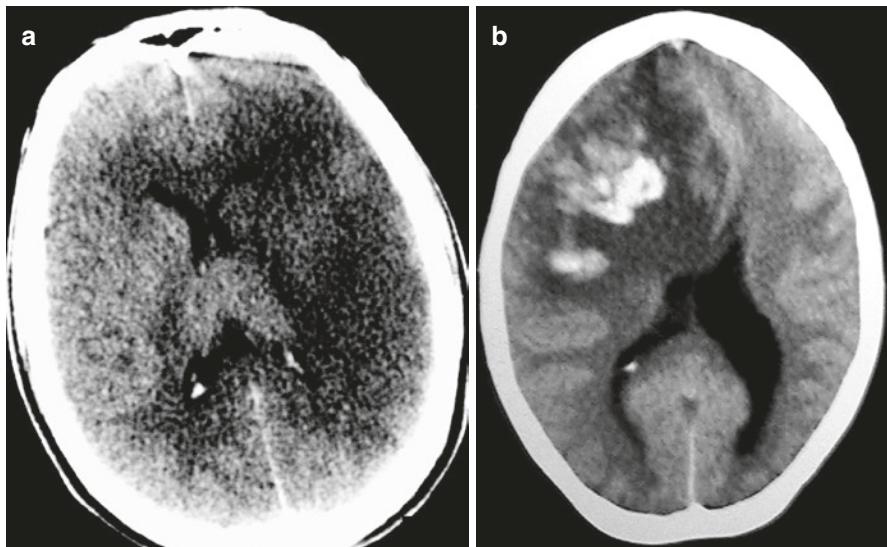


Fig. 13.1 (a) NCCT head reveals a large left middle cerebral artery infarct. (b) Sagittal sinus thrombosis. NCCT head reveals a frontal haemorrhagic venous infarct in a patient with superior sagittal sinus thrombosis

Involvement of the transverse sinus leads to temporoparietal lobe infarction (Fig. 13.2). Unilateral or bilateral infarction of the basal ganglia, thalamus and internal capsule may be seen typically in thrombosis of the deep venous system (Fig. 13.3).

Neuroimaging

In the emergency setting, a plain CT scan provides invaluable clues to the diagnosis of CVT. Findings on a plain CT may be confirmed on a contrast-enhanced scan. Important signs are given in Table 13.5. Notably, in rare cases, CVT may present with isolated subarachnoid haemorrhage. Dural sinus thrombosis with secondary venous hypertension may lead to SAH into the subarachnoid space due to the rupture of fragile, thin-walled cortical veins. In a typical case of SAH presenting with a thunderclap headache, CVT may be diagnosed on CT angiography or based on subtle signs on the plain CT itself. In a series of 332 patients with CVT, 10% (33) cases presented with SAH [18]. Of these 33 patients, 22 presented with pure SAH in the absence of any haemorrhagic infarct. CVT involved lateral sinus in 18

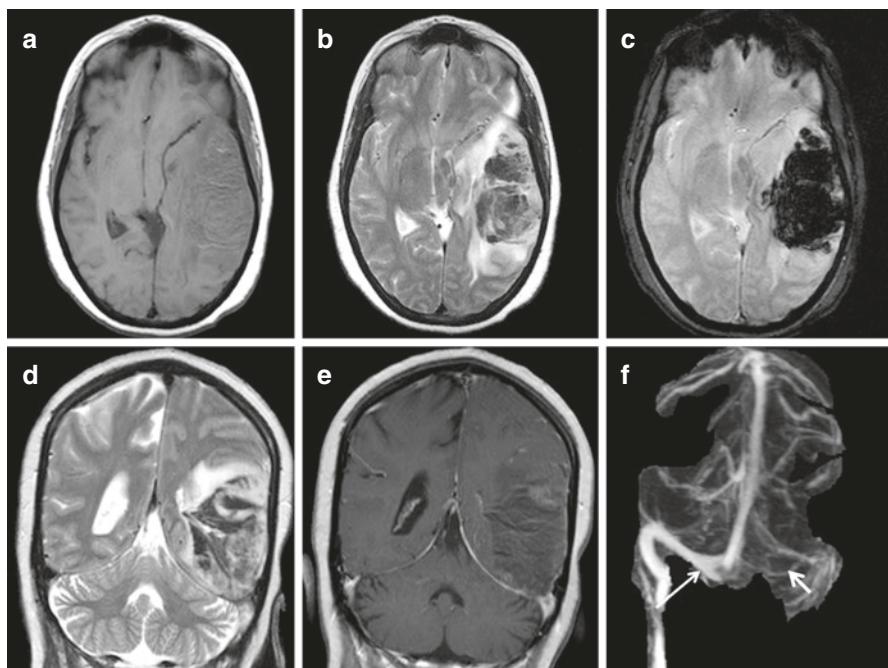


Fig. 13.2 Lateral sinus thrombosis. MR scan head reveals a venous infarct in the left parietal-temporal region appearing as a hypointense area on T_1W (a, e), heterogeneous on T_2W (b, d) with evidence of haemorrhage on gradient image (c). Contrast-enhanced MR venogram (f) reveals occlusion of the left transverse sinus (small arrow), sigmoid sinus and jugular vein, and normal-looking right transverse sinus (long arrow), sigmoid sinus and jugular vein

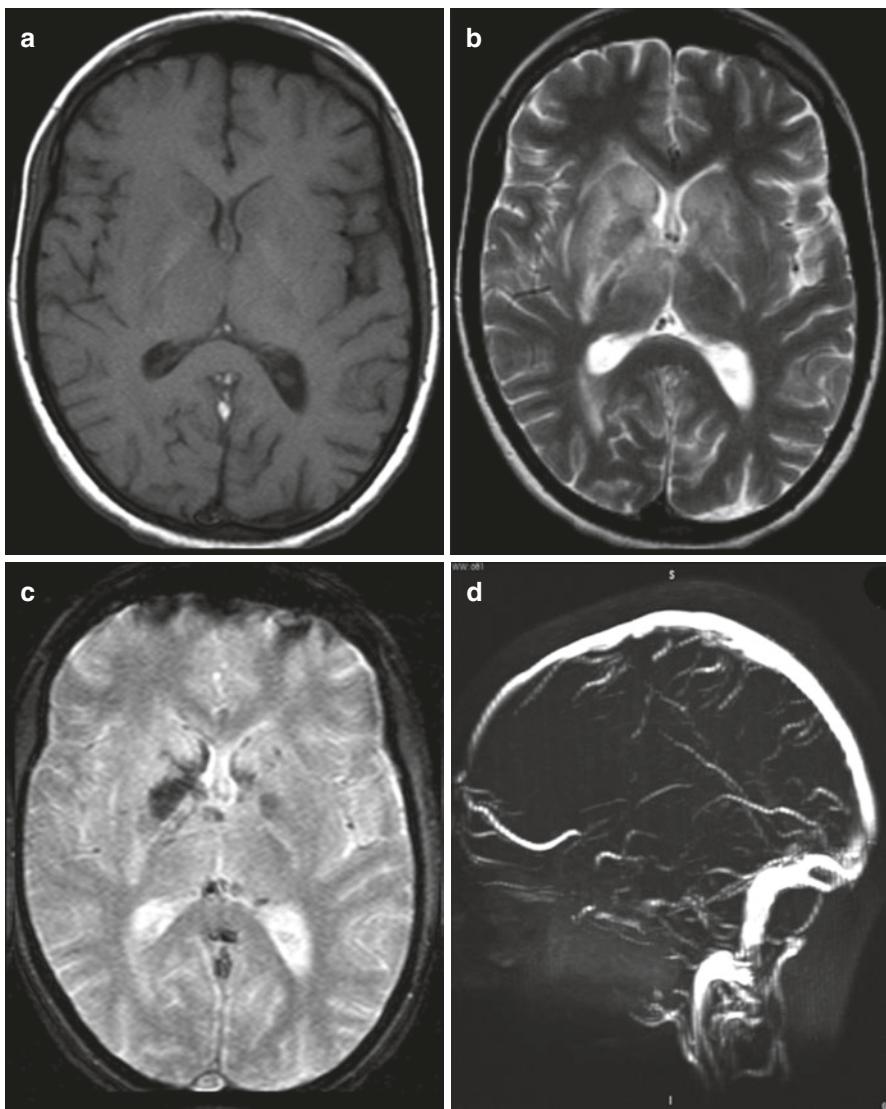


Fig. 13.3 Deep venous thrombosis. MR scan head. T_1W image (a), T_2W (b) shows signal changes in bilateral basal ganglia and presence of haemorrhage on gradient echo image (c, arrow). There is a thrombus in the internal cerebral vein and straight sinus appearing as a hyperintense signal on T_1W image (a, arrow). Contrast-enhanced MRV (d), shows absence of signal in the region of the internal cerebral veins and straight sinus

patients, superior sagittal sinus in 16 and straight sinus in 1. Cortical veins were involved in all patients, in continuity with dural sinus thrombosis when present. SAH was circumscribed to few sulci in all cases and mainly localized at the convexity (21 cases). Therefore, unless CVT is systematically considered in the

Table 13.5 Imaging features in cerebral venous thrombosis

Signs	Pitfalls
Non-contrast CT	<p>1. Dense clot sign—thrombus seen directly in a dural venous sinus (Fig. 13.4)</p> <p>2. Cord sign—thrombus seen as hyperdensity in a cortical vein</p> <p>3. Indirect signs—diffuse brain oedema, leading to hypodensity of the brain or decreased ventricular size</p> <p>4. Deep venous thrombosis (involved in 10% of cases [17])—unilateral or, more typically, bilateral venous congestion and venous infarction of the thalamus and basal ganglia (Fig. 13.3)</p>
Contrast-enhanced CT	<p>1. Empty delta sign—represents a filling defect (thrombus) in the dural sinus, with peripheral enhancement secondary to the development of collaterals (Fig. 13.5)</p> <p>2. Indirect evidence of CVT may be seen as contrast enhancement of the falx and tentorium secondary to venous stasis and hyperaemia of the dura mater</p>
MRI	<p>1. Acute thrombus is isointense to the brain on T_1-weighted images and hypointense on T_2-weighted images (Fig. 13.6). From 3 to 7 days after thrombus formation, it is easier to recognize the clot on MRI, because it becomes hyperintense on T_1-weighted images (Fig. 13.7)</p>

workup of patients presenting with SAH of the cerebral convexity, it may be missed.

In a suspicious case, the diagnosis should be confirmed by more sensitive imaging techniques, such as MRI and MRV (Tables 13.5 and 13.6). Conventional MR sequences show patent dural sinuses as flow voids. Coronal images are best for visualization of the superior, transverse and sigmoid sinuses. A plane parallel to the dural sinus offers better depiction of the extent of the thrombus in the dural sinus.

It is important to note that in 10–30% of cases of CVT, the findings on either unenhanced or contrast-enhanced CT are negative (Figs. 13.4 and 13.5) [19]. In the acute stage, the thrombus may be seen as isointense on T_1 -weighted but hypointense on T_2 -weighted MRI sequences (Fig. 13.6). In such a situation, either a gradient sequence or an MRV is warranted, the latter being the investigation of choice (Figs. 13.6 and 13.7).

Table 13.6 Comparison of magnetic resonance venography techniques

Technique	Advantages	Disadvantages
Time-of-flight	Shorter imaging time	More prone to false-positive results from in-plane flow False-negative results due to methaemoglobin
Phase-contrast	Better background suppression Can detect flow in all three orthogonal planes Better flow quantification No false-negative results due to methaemoglobin	More sensitive to motion artefacts and turbulent flow
Gadolinium-enhanced	Less likely to give false-positive results due to slow or complex flow	Potential false-negative results due to methaemoglobin or enhancing chronic thrombosis

Adapted from Colin et al. Radiologic diagnosis of cerebral venous thrombosis: Pictorial review. *AJR Am J Roentgenol* 2007 [19]

Fig. 13.4 Dense clot sign.
NCCT head reveals hyperdensity in the region of the posterior interhemispheric fissure suggestive of thrombus in the sagittal sinus (lines) and straight sinus (line)



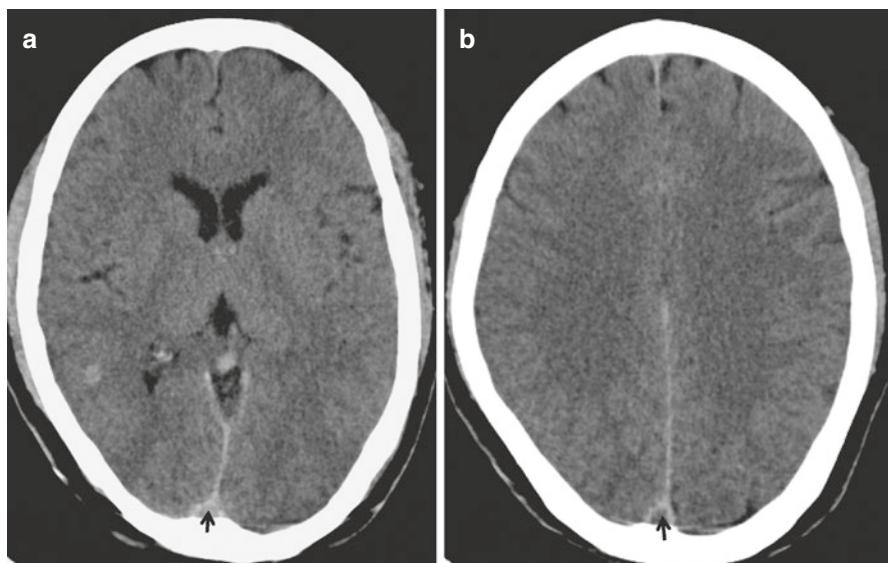


Fig. 13.5 (a, b) Empty delta sign. Contrast-enhanced CT (CECT) head reveals a filling defect in the region of superior sagittal sinus (*arrow*)

Vascular Imaging

Vascular imaging includes MRV, CTV (CT venography) and conventional angiography.

MRV is most commonly used to confirm the diagnosis of CVT in a suspected case, especially in the acute stage, as the direct visualization of the thrombus may be difficult on MRI (thrombus being isointense on T_2). Contrast MRV is preferred although it may also be performed without the use of a contrast agent using the time-of-flight technique or the phase-contrast technique (Table 13.6). Because these techniques use MR flow phenomena for contrast generation, they are subject to flow-related image artefacts.

64-slice multidetector-row computed tomography (MDCT) and CT venogram have been used in some centres for the diagnosis of venous sinus thrombosis and found to be 100% sensitive and specific [20]. Cerebral catheter angiography is rarely used for the diagnosis of CVT; conventional angiography best demonstrates the dynamics of the intracranial circulation [21]. Venous collateral circulation is also best appreciated on conventional angiography. Dilated, tortuous collateral veins develop in the setting of chronic venous hypertension related to veno-occlusive disease. This constellation of findings on the venous phase of the angiogram has been referred to as a 'pseudophlebitic pattern'. The ability to develop a venous collateral circulation accounts for the variable clinical presentations and unpredictable outcome of CVT. Further details on imaging in CVT are given in Chap. 2.

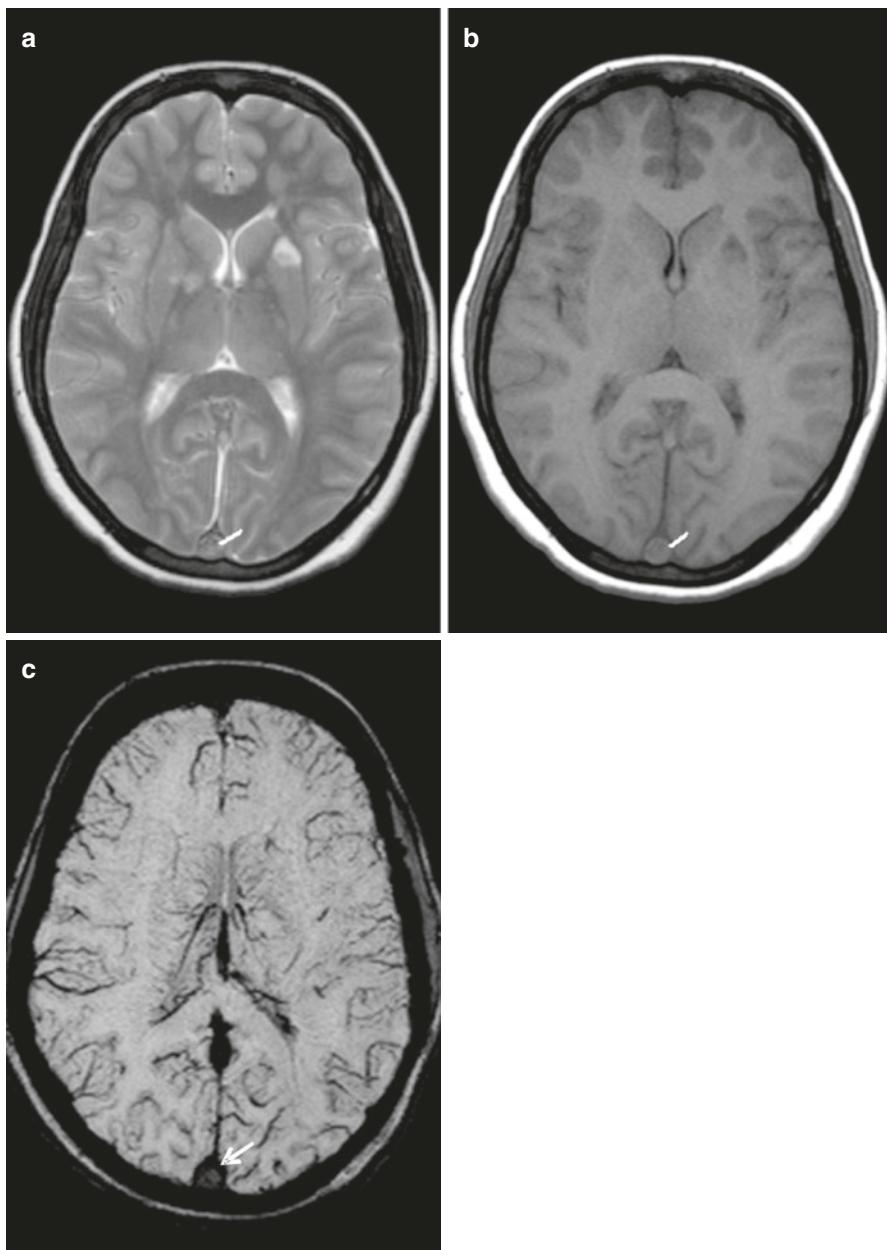


Fig. 13.6 Acute sagittal sinus thrombosis. Thrombus is seen as hypointense on T2W (a) and hypointense on T1W (b) images (lines). The thrombus is also appreciated on the susceptibility-weighted image (SWI) (c, arrow)

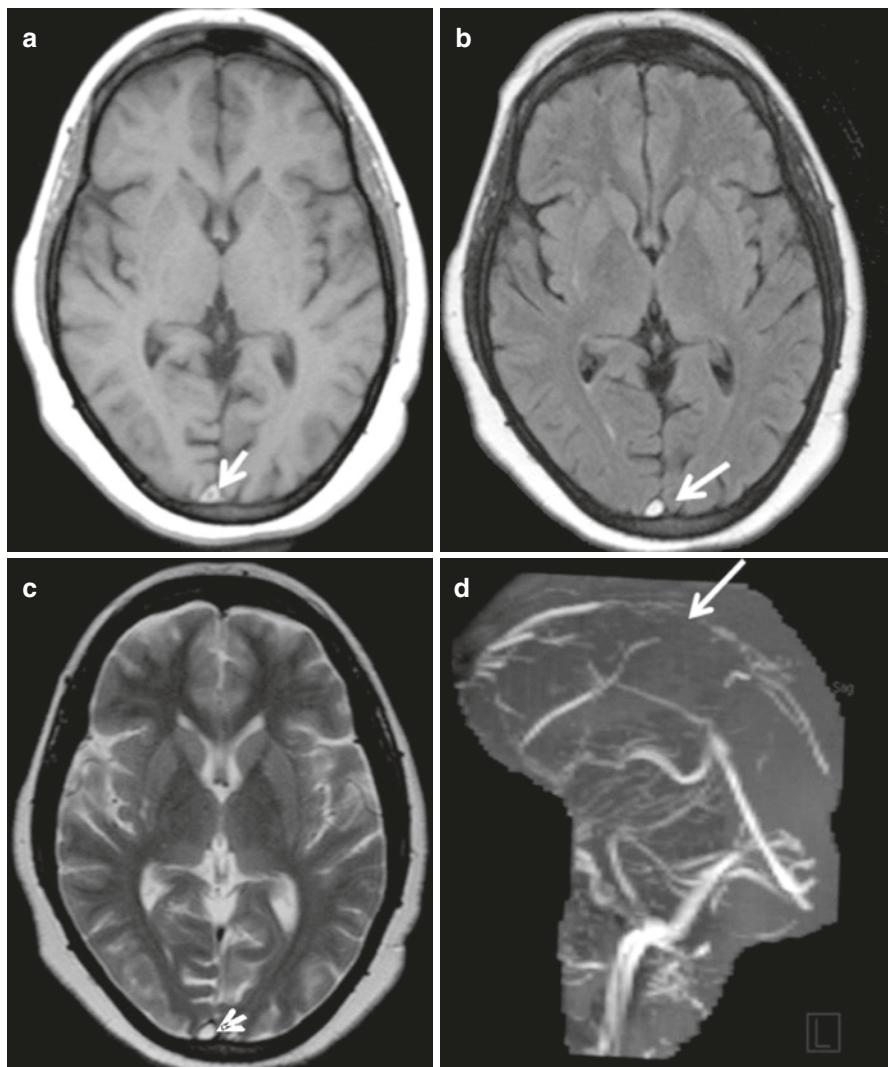


Fig. 13.7 Sagittal sinus thrombosis, subacute stage. MR scan reveals hyperintensity in the region of the superior sagittal sinus appearing bright on T_1W (a, small arrow) and FLAIR (b, long arrow). There is absence of the normal flow void on T_2W images (c, arrow). MR venogram (d) reveals a filling defect in the superior sagittal sinus (arrow)

Management of CVT

Once the diagnosis of CVT is established, management in the emergency setting is aimed at two major objectives: symptomatic management and prevention of propagation of the thrombus. Management of chronic CVT presenting as IIH is outside the purview of the present discussion.

Symptomatic Therapy

Managing Raised ICT

The priority of treatment in the acute phase is to lower the ICP, avert its detrimental effects and, importantly, to prevent or reverse cerebral herniation. This may require head elevation at 10°–20°, intravenous use of osmotic diuretics including mannitol (Table 13.7), hypertonic saline and decompressive haemicraniectomy.

However, osmotic agents should be used with caution as they are not quickly eliminated from the intracerebral circulation and their use may be associated with volume contraction secondary to diuresis, which may further enhance the thrombotic process. Volume restriction should thus be avoided. Hypertonic saline has been in clinical use for many decades. Its osmotic and volume-expanding properties make it theoretically useful for a number of indications in critical care [22]; 3% hypertonic saline has been used in stroke patients instead of, and not in conjunction

Table 13.7 Management of CVT

Management of CVT—symptomatic therapy

1. Lowering intracranial pressure

- (a) Head elevation to 10°–20°; ensure there is no venous compression
- (b) Inj. mannitol (20%): 0.5 g/kg over 15 min for up to three doses or until osmolality has reached 320 mosm/L—whichever is first
- (c) Hyperventilation: may be used when standard treatment fails
- (d) 3%–5% intravenous saline: may be useful in hypotensive patients
- (e) Decompressive haemicraniectomy (see also Chap. 27 on ‘Neurosurgical interventions in neurological emergencies’)

2. Management of seizures

- (a) Choice of antiepileptic medication: start with intravenous loading dose of first-line AED, i.e. inj. phenytoin sodium 20 mg/kg in saline at a rate not exceeding 50 ml/min or inj. valproate—25–30 mg/kg in 100 ml normal saline i.v. over 20 min, followed by maintenance doses
If patient has presented in status, manage with standard therapy for status epilepticus.
(See also Chap. 8 on ‘Acute seizure emergencies’)
- (b) Antiepileptic medication is indicated in:
 - (i) Acute phase in patients with acute seizures and in patients with focal parenchymal lesions or with focal neurological deficits
 - (ii) Prevention of seizures after the acute phase in patients who present with acute seizures and in those with focal haemorrhagic lesions

Management of CVT—antithrombotic therapy

1. Heparin

- (a) LMWH: 180 anti-factor Xa U/kg/24 h—subcutaneously twice a day
- (b) Dose-adjusted i.v. heparin to keep activated partial thromboplastin time (APTT) at twice the control value (see Table 13.8)

2. Oral anticoagulation

- (a) Oral anticoagulation (maintaining INR at 2–3) for 3 months in patients with identifiable/reversible cause
- (b) In idiopathic CVT, extracerebral venous thrombosis and mild hereditary thrombophilia continue oral anticoagulation for 6–12 months

3. Thrombolytic therapy

Local thrombolytic therapy and mechanical clot removal may be tried in refractory cases in experienced centres

with, mannitol. Hypertonic saline may be preferred in a hypovolaemic and hypotensive patient. The adverse effects of hypertonic saline include bleeding secondary to decreased platelet aggregation, prolonged coagulation time, hypokalaemia and hyperchloraemic acidosis. Steroids have failed to show any benefit in the management of CVT [23]. **In patients with CVT and increased intracranial pressure, it is reasonable to initiate treatment with acetazolamide. Other therapies (lumbar puncture, optic nerve decompression or shunts) can be effective if there is progressive visual loss.**

In severe cases with threatening transtentorial brain herniation caused by a large haemorrhagic infarct, decompressive surgery may be the only way to save the patient's life. This has been covered in detail in Chap. 27 on 'Neurosurgical interventions in neurological emergencies'. In a series of three patients with fixed dilated pupils caused by transtentorial herniation who underwent decompressive haemisplenectomy, two recovered with only minor neurological sequelae [24]. The haemorrhagic infarct should not be removed because neuronal damage is often less pronounced in CVST-related haemorrhage, explaining the possible reversal of even severe clinical symptoms [25]. In a series of seven patients from Pakistan who underwent decompressive craniectomy for CVT, four had an excellent outcome, two died and one of the seven was lost to follow-up [26]. A large international multicentric registry on decompressive craniectomy in patients with CVT is ongoing.

Management of Seizures

A recently published study identified focal sensory deficits and the presence of focal oedema or ischaemic/haemorrhagic infarcts on the admission CT/MRI as significant predictors of early symptomatic seizures [27]. Prophylactic treatment with an antiepileptic drug (AED) may be a therapeutic option in these patients. It is, however, not warranted in the absence of focal neurological deficits and/or focal parenchymal lesions on brain imaging (e.g. patients with IIH). Prolonged treatment with AEDs for 1 year may be reasonable for patients with early seizures and haemorrhagic lesions on admission brain scan, whereas in patients without these risk factors, AED therapy may be tapered off after the acute stage.

Antithrombotic Therapy

Arterial stroke leads to cytotoxic oedema and progressive loss of penumbral tissue, whereas the principal tissue pathology of venous occlusion is vasogenic oedema. It may seem intuitive that recanalization would assist in recovery from venous occlusion. These plausible explanations led to the use of intravenous heparin in CVST regardless of the presence of intracranial haemorrhage. However, another school of thought postulates that recanalization may have little bearing on the outcome in a process that develops slowly so that the entire survival decision may be based on the presence or absence of adequate collaterals. Anticoagulant treatment has raised much controversy because of the tendency of venous infarcts to become

haemorrhagic: ~40% of all patients with sinus thrombosis have a haemorrhagic infarct even before anticoagulant treatment is started [28].

Heparin Therapy

Two randomized trials and one meta-analysis of heparin treatment for CVST have been performed [29–31]. Both trials showed a consistent and clinically meaningful trend in favour of anticoagulation (AC) and demonstrated the safety of anticoagulant therapy.

Current evidence therefore shows that patients with CVST without contraindications for AC should be treated either with body weight-adjusted subcutaneous low-molecular-weight heparin (LMWH) (180 anti-factor Xa U/kg/24 h administered by two subcutaneous injections daily) or dose-adjusted intravenous heparin with an at least doubled activated partial thromboplastin time (aPTT) (level of evidence 1a). The protocol for the use of conventional heparin is given in Table 13.8.

It is unclear whether treatment with full-dose intravenous heparin or subcutaneous LMWH is equally effective for CVST. Advantages with LMWH include the route of administration, which increases the mobility of patients, and the lack of laboratory monitoring and subsequent dose adjustments. A possible advantage of dose-adjusted intravenous heparin therapy, particularly in critically ill patients, may be the fact that the aPTT normalizes within 1–2 h after discontinuation of the infusion if complications occur or surgical intervention becomes necessary. In the recent analysis of the ISCVT data, the authors compared the non-randomized data of the two heparin regimens used for the treatment of patients [32]. Although there was no difference in the mortality and complete recovery among the two groups, the authors concluded that there was a suggestion of a better efficacy and safety of LMWH over unfractionated heparin and that LMWH seemed preferable to unfractionated heparin for the initial treatment. However, these findings need to be studied in a randomized trial.

Role of Oral Anticoagulants

The role of oral anticoagulant therapy in CVST remains uncertain [33]. Analogous to patients with extracerebral venous thrombosis, oral AC with a target INR of 2.0–3.0 may be given for 3 months if CVST was secondary to a transient (reversible) risk factor and for 6–12 months if it was idiopathic. Oral AC is also recommended for 6–12 months in patients with extracerebral venous thrombosis and a mild

Table 13.8 Heparin protocol for cerebral venous sinus thrombosis (CVST)

Initial infusion: 18 U/kg/h i.v.; aPTT checked at 6 h and q 6 h after any dosage change, as well as every morning; adjust dose according to the following parameters:

- aPTT = <1.2 times control: 80 U/kg bolus with increase of 4 U/kg/h
- aPTT = 1.2–1.5 times control: 40 U/kg bolus with increase of 2 U/kg/h
- aPTT = 1.5–2.3 times control: No change in infusion rate needed
- aPTT = 2.3–3 times control: Decrease infusion rate by 2 U/kg/h
- aPTT = >3 times control: Hold infusion for 1 h and decrease rate by 3 U/kg/h

aPTT activated partial thromboplastin time

hereditary thrombophilia, such as protein C and S deficiency, heterozygous factor V Leiden or prothrombin G20210A mutations. Long-term treatment should be considered for patients with a severe hereditary thrombophilia, which carries a high risk of recurrence, such as antithrombin deficiency, homozygous factor V Leiden mutation or two or more thrombophilic conditions. Indefinite AC is also recommended in patients with two or more episodes of idiopathic, objectively documented extracerebral venous thrombosis. In patients who demonstrate progressive neurological deterioration despite adequate AC, other options, such as local intrathrombus infusion of a thrombolytic agent together with intravenous heparin, are under investigation. The ongoing EXCOA-CVT (the benefit of EXtending oral antiCOAgulant treatment after Cerebral Vein and Dural Sinus Thrombosis) is a prospective randomized study to compare short- (3–6 months) versus long-term (12 months) oral anti-coagulation in the prevention of VTEs after an episode of CVT [34].

Role of Intrasinus Thrombolysis

The literature lacks established indications pertaining to intravascular thrombolysis in CVST. The use of local thrombolysis was first reported by Scott et al. in 1988 [35]. They infused urokinase through a burr hole directly over the superior sagittal sinus. This led to a rapid recovery in a patient in coma with mild residual aphasia and memory impairment. Endovascular thrombolysis (with or without mechanical thrombus disruption) is an experimental treatment to be used in experienced centres for severe cases or in patients who fail to improve on AC, possibly without coexisting intracranial haemorrhage. Local thrombolysis is not useful in patients with large infarcts and impending herniation. The use of either heparin and urokinase or heparin and recombinant tissue plasminogen activator (which may carry less bleeding complications due to its clot selectiveness and shorter half-life) has been described in the literature. Although there is no established regimen, conventionally (based on recent case series) a bolus dose of 10,000 units of urokinase was given followed by 100,000 units/h for periods varying from 6 to 24 h [36, 37]. Oral AC is continued for at least 6 months even in these patients [29]. Early therapeutic intervention may lead to successful clot lysis while it is still in a friable state. On the contrary, chronic lesions prove resistant to lysis. In a recent systematic review of the literature on the safety of thrombolysis in CVT [38], the authors concluded that there are safety concerns for this therapy, and more data are needed to compare thrombolytic therapy with standard conservative therapy.

Kumar et al. reported that 19 patients received intrasinus thrombolytic therapy in which clinical deterioration continued in the form of rapid worsening of consciousness or aggravation of neurological deficits despite adequate AC. At discharge, 79% patients had a good outcome and were either asymptomatic or had only mild deficits and were independent for activities of daily living. Three patients died, and one survived with severe neurological deficits [37]. Mechanical thrombectomy may also be attempted along with thrombolysis. Haghghi et al., in a systematic review to evaluate the role of mechanical thrombectomy, reported that 62.5% patients had no or minor disability, 10.9% had a major disability and 16.1% died after such procedures [39].

Management of Complications

All patients should be carefully monitored for complications, such as aspiration, urinary tract infection (UTI), bed sores, deep vein thrombosis (DVT), pulmonary embolism, electrolyte imbalance, etc. Standard therapy, as required for individual complications, should be provided. Nutrition should be carefully monitored.

Patients with CVT and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVT when appropriate.

Prognosis and Outcome

The long-term prognosis after CVT and sinus thrombosis mainly depends on the underlying disease, e.g. cancer or a known prothrombotic state. If no serious underlying disease is present, the long-term prognosis is generally good. However, impaired functional outcome, headaches, epileptic seizures, cognitive impairment, recurrent thrombosis and death occur in some patients. In a study, independent predictors of mortality due to CVST included coma, age older than 37 years, deep CVST, right intracerebral haemorrhage, posterior fossa lesion, worsening of previous focal deficits or de novo focal deficits, haemorrhage on admission CT, central nervous system infection and cancer [40].

Conclusion

CVST is a rampant yet under-recognized entity in the practice of neurology. It accounts for a substantial proportion of strokes in the young, and post-partum CVT is particularly common in India. Diagnosis calls for a high degree of suspicion in a patient presenting with stroke without conventional vascular risk factors. Treatment is aimed at averting the detrimental effects of raised ICP and preventing the complications thereof.

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Diagnosis and Treatment of Meningitis

14

Elizabeth W. Kelly and Michael T. Fitch

Introduction

Meningitis is an inflammatory process of the membranes and fluids that surround the brain and spinal cord, including the arachnoid, pia mater and surrounding cerebrospinal fluid (CSF). From its recognition in the early 1800s to the beginning of the twentieth century, bacterial meningitis was nearly 100% fatal [1]. Although antibiotics have made the disease curable [2, 3], morbidity and mortality remain high throughout the world, even with appropriate treatment [1, 4]. Meningitis can occur in healthy individuals and can strike at any age. However, patients at the extremes of age (young children and the elderly) and those who are immunosuppressed are at increased risk [5]. Infants who survive Gram-negative bacterial meningitis have a high rate of developmental and neurological sequelae [6]. The overall case fatality rate of bacterial meningitis in adult patients is 13–27% [4, 7–14].

It is important for emergency medicine, primary care and other healthcare providers to accurately diagnose this life-threatening condition and promptly administer appropriate antibiotics and consider other adjunctive therapies [15]. In the acute care setting, it is often difficult to distinguish bacterial meningitis from meningitis due to other causes, such as viruses, fungi and neoplastic, toxic and autoimmune processes. Once the diagnosis of meningitis has been made and if the aetiology remains unclear, empirical treatment should be promptly initiated to treat for possible bacterial meningitis while awaiting culture results or the results of other confirmatory tests.

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Incidence

Bacterial meningitis occurs throughout the world; though in many countries where specific studies have not been completed, the exact incidence is unknown. The disease occurs more frequently among males than females and is most common in the late winter and early spring [16]. There has been a recent decline in the incidence of meningitis in the USA secondary to the widespread use of new vaccines [5]. In the early 1990s, the conjugated *Haemophilus influenzae* type B vaccine was introduced in the USA, and, in 2000, the US Food and Drug Administration approved the use of the *Streptococcus pneumoniae* vaccine [5]. In the USA, the incidence of bacterial meningitis in the post-vaccine era is estimated at 2–10 cases per 100,000 population per year [5, 17, 18], although attack rates are very age-specific. The incidence is the greatest in infants, with a neonatal attack rate of about 400 per 100,000, compared to 1–2 per 100,000 in adults and 20 per 100,000 in children less than 2 years of age [19]. The rate of infection can be as much as 10 times higher in developing nations [7, 13, 14, 18, 20]. In the USA and other developed countries, epidemics of acute meningococcal meningitis can occur, whereas in parts of sub-Saharan Africa (referred to as the meningitis belt), meningococcal meningitis is endemic [21]. These endemic cases usually occur in the dry season, the annual rate being about 500 cases per 100,000, and they typically occur in areas with poor access to medical care [22]. Epidemics of meningococcal disease most commonly occur in areas where many people live together for the first time, such as in army barracks and college campuses [23], or during the large annual Hajj pilgrimage to Mecca [24].

Viral infections are the more common cause of aseptic meningitis, although the incidence is relatively difficult to estimate as many cases are not reported. Viral meningitis occurs more commonly in the summer months, and some epidemiology studies have estimated that these infections occur in the range of 11–27 cases per 100,000 people [25].

Tuberculous meningitis is the most common cause of chronic meningitis [26] and this condition kills or disables more than half of those affected [27]. The incidence of tuberculous meningitis is directly related to the incidence of tuberculosis (TB) in the community and, therefore, occurs most frequently in places such as Africa and Southeast Asia, where the incidence of TB is the highest [27, 28]. An in-depth discussion of tuberculous meningitis is beyond the scope of this chapter, and readers are referred to other recent reviews of this cause of CNS disease [29].

Causes

By convention, meningitis is classified as bacterial when caused by an infection by such a pathogen or aseptic when the inflammation is due to other causes, such as drugs, rheumatological conditions or nonbacterial infections.

The most common pathogens to cause bacterial meningitis are encapsulated organisms that typically invade the host through the upper airway after initially colonizing the nasopharynx [30]. The organism invades through the mucosa and

enters the bloodstream and ultimately crosses the blood–brain barrier and proliferates in the CNS [30]. The routes of entry can also include direct CNS inoculation after surgery or trauma [5, 30]. The other factors that can contribute to a pathogen gaining entry into the CSF include contiguous infection (e.g. sinusitis, mastoiditis or otitis media), haematogenous seeding of the CSF (e.g. intravenous [i.v.] drug abuse or bacterial endocarditis) and congenital defects [5]. See Table 14.1 for a summary of common aetiologies of bacterial meningitis.

In recent years, the epidemiology of bacterial meningitis has changed considerably. Today, the most common causes include *Streptococcus pneumoniae* and *Neisseria meningitidis* [4, 13, 14, 18, 31]. Meningitis due to *Haemophilus influenzae* type b decreased dramatically since routine childhood vaccination against *H. influenzae* type b was initiated [18, 32], and the recent use of pneumococcal vaccine is preventing disease in young children who receive the vaccine and may be reducing the rate of disease in adults by herd immunity [33]. The use of these vaccines has also been suggested to be an effective means of reducing disease caused by drug-resistant strains [33]. Given the effectiveness of the vaccines in young children, it is not surprising that the median age of persons with bacterial meningitis has increased. In 1986, the median age of persons with bacterial meningitis in the USA was 15 months, as compared to 25 years in 1995, 30 years in 1998–1999 and 42 years in 2006–2007 [4, 18]. This change in age distribution has been attributed in part to the large decline in the number of cases of *H. influenzae* meningitis [18].

Neisseria meningitidis is a frequent cause of bacterial meningitis and other invasive bacterial infections such as meningococcaemia throughout the world [34]. Its role has become more pronounced in recent years not only due to new conjugate vaccines against *H. influenzae* and *S. pneumoniae* but also owing to a decline in meningitis secondary to group B streptococcus due to prophylactic intrapartum antibiotics [32, 35]. There has also been a decline in meningitis caused by *Listeria*

Table 14.1 Aetiology of bacterial meningitis [7, 8, 10, 13, 21]

Aetiology	Mechanism of infection
Encapsulated organisms colonization of nasopharynx	Invade host through upper airway followed by bloodstream and then CNS invasion
Complication of surgery or trauma	Direct CNS inoculation
Recent host infection such as sinusitis, mastoiditis and otitis media	Contiguous infection
Intravenous drug abuse or bacterial endocarditis	Haematogenous seeding of CSF
Congenital defects such as cranial and cervical anatomical defects	Anatomy of host predisposes to CSF infection
Medical device such as CSF shunt, intracerebral pressure monitor, cochlear implants with positioners	Direct entry into CNS
Immunocompromised host factors including asplenia, complement deficiency, glucocorticoid excess, diabetes mellitus and alcoholism	Predispose host to infection

monocytogenes due to efforts to reduce food contamination with this pathogen. Disease caused by *L. monocytogenes* is more common in older patients (>50 years old), infants (<3 months old), and immunocompromised or pregnant individuals [1]. Meningococcal C vaccine (MCC) was introduced in the United Kingdom in 1999 and in six other European countries between 2000 and 2002, and all these countries have seen a decline in meningococcal disease since then [36]. Hopefully, this trend will continue as vaccines for meningococcal disease become more widely used throughout the world. Polysaccharide vaccines to additional serogroups have been developed and shown to be efficacious [37] and are now part of routine vaccination schedules in some countries [38].

Aseptic meningitis is due to a meningeal irritation where a pyogenic bacterial source is not the cause. The term is a misnomer since most cases of aseptic meningitis are caused by viral infections or mycobacterial infections. The number of cases of viral meningitis that occur annually exceeds the total number of meningitis cases caused by all other aetiologies [39]. Enteroviruses, such as Coxsackie and echoviruses, remain the most common cause of aseptic meningitis, comprising more than 80% of all cases [40–42]. Another common cause is herpes simplex virus (HSV) infection, specifically HSV-2 [43]. Other less common causes in immunocompetent hosts include mumps, HIV, cytomegalovirus and varicella zoster virus [20]. Other infectious causes of aseptic meningitis that do not grow in routine CSF bacterial cultures include *Mycobacterium tuberculosis*, *Treponema pallidum*, *Borrelia*, *Chlamydia*, *Mycoplasma* species, *Rickettsia*, fungi (such as *Cryptococcus* sp., *Coccidioides* sp. and *Histoplasma* sp.) [44], protozoa and malaria [20, 44–50]. Non-infectious causes of meningitis can include malignancy, sarcoidosis and immune diseases [20, 51]. Cases of drug-induced aseptic meningitis have also been documented, and the offending agents include trimethoprim, non-steroidal anti-inflammatory drugs, intravenous immunoglobulin and numerous antibiotics [45, 52]. The other causes include rheumatological disorders, such as Sjögren syndrome [51], and meningitis associated with vaccines such as the measles–mumps–rubella vaccine [20, 53].

Clinical Features

The classic clinical triad of meningitis includes fever, neck stiffness and altered mental status, but in some studies this triad is present in less than half of adult patients with bacterial meningitis [5, 14]. Many of the symptoms of meningitis, such as headache, nausea and vomiting and neck pain, are non-specific, and this makes diagnosis a considerable challenge. Patients at the extremes of age are often diagnostic dilemmas as neonates and the elderly can have very subtle presentations, and some of these patients, as well as those who are immunocompromised or partially treated with antibiotics, may not present with fever [5]. Infants may be hypothermic or afebrile and may not have neck stiffness. Among infants, the chief complaints are often non-specific and include irritability, lethargy, poor feeding, apnoea, rash or a bulging fontanelle [54].

Classically described meningeal findings include nuchal rigidity (severe neck stiffness caused by meningeal irritation), Kernig's sign (pain in the back and legs on flexion of the hip and extension of the knee) and Brudzinski's sign (flexion of the hips on passive flexion of the neck) [20]. However, the clinical utility of these findings is uncertain due to their poor sensitivities, which are only 5–30% [55–57]. Some studies indicate that neck stiffness may only be present 30% of the time in patients with meningitis [58]. Given these low sensitivities, absence of these findings cannot be used in isolation to exclude meningitis as a diagnostic possibility. However, the specificity of Kernig's and Brudzinski's signs at 87–100% suggests that these are concerning findings when assessing patients for potential CNS infection [55–57, 59]. Jolt accentuation, which has been described as the exacerbation of a baseline headache with horizontal rotation of the neck, is a physical exam finding that has been proposed to evaluate for meningeal irritation, and several small studies have reported similar sensitivity (21%) and specificity (82%) [60].

Other symptoms that may be present in patients with meningitis include confusion, abnormal mental status or seizure. Older patients with this infection often present with confusion or altered mental status [61]. Seizures have been shown to occur in 5–28% of adults who have meningitis [7, 10, 62] and are the presenting symptom in about one-third of children with bacterial meningitis [63]. Although petechiae and purpura are classically associated with meningococcal meningitis, these skin findings can be present with other causes of bacterial meningitis or may be absent in many patients [64].

Investigations

CSF Analysis

Analysis of CSF is an important aspect for making the diagnosis of meningitis, and, therefore, a lumbar puncture (LP) is indicated for patients suspected of having this diagnosis. Minor complications of this procedure may include a post-LP headache, bleeding at the site of puncture and local back pain. One rarely reported complication is brain herniation, although the causal relationship between LP and herniation remains an area of debate. This devastating complication has been reported in the literature since the first LPs were performed in the late 1800s [65]. Of the utmost concern is the possible presence of an occult mass from infections such as toxoplasmosis or from a brain tumour, which may precipitate herniation and subsequent death [15]. In spite of many case reports and studies on the topic, a clear relationship between LP and herniation has never been proven. However, a CT scan of the brain is recommended to screen for contraindications to LP under the following circumstances: altered mental status, new-onset seizures, an immunocompromised state, focal neurological signs or papilloedema [15, 66]. A recent initiative by one group in Sweden removed impaired mental status as a contraindication for LP prior to CT scan to decrease delays in antibiotic treatment [67, 68], although concerns about missing other potential diagnoses have been raised [69]. A CT should also be

considered for patients with risk factors for intracranial lesions, such as brain abscesses or malignancy [20].

When an LP is performed, four tubes of CSF, each containing about 1–2 mL of fluid, are typically obtained. The diagnostic tests commonly ordered are cell count and differential, protein and glucose levels and Gram stain and culture. (See Table 14.2 for an overview of classically described CSF findings in various forms of meningitis.) Elevated numbers of white blood cells in the CSF are diagnostic of meningitis. The other CSF findings that are suggestive of bacterial meningitis include the following:

- Positive Gram stain with identified organism
- Glucose < 40 mg/dL or ratio of CSF/blood glucose < 0.40
- Protein > 200 mg/dL
- WBC > 1000/mL
- Polymorphonuclear neutrophils > 80%
- Elevated opening pressure of CSF during LP

Other disease processes that can give abnormal CSF findings and pleocytosis include tuberculous meningitis, brain abscesses, neoplasms, viral meningitis, fungal meningitis and any other cause of aseptic meningitis. (Please refer to Chap. 3 for a detailed discussion on the CSF.)

It is important to remember that the CSF findings in bacterial meningitis do not always yield classical results, and this can lead to challenges to prospectively predict whether a case of meningitis is caused by a bacterial infection or a potentially more benign aseptic cause. There are rare case reports of patients with bacterial meningitis where initial CSF findings did not show pleocytosis but organisms later grew from the CSF sample and many of these infections were caused by *S. pneumoniae* or *N. meningitidis* [70].

In the presence of CSF pleocytosis, there is no single variable that reliably rules out bacterial meningitis with complete certainty [7, 14]. There are several factors that can have an impact on the CSF results, including partially treated meningitis (patient on prior antibiotics), the timing of the LP (early in the course of disease versus late), the patient being immunocompromised or there being an

Table 14.2 Classically described cerebrospinal fluid findings in bacterial, viral and fungal meningitis

CSF findings	Meningitis		
	Bacterial	Viral	Fungal
Opening pressure	Elevated	Normal	Elevated
White blood cell count	1000–10,000	<300	<500
Neutrophils	>80%	1–50%	1–50%
Glucose	Reduced	Normal	Reduced
Protein	Elevated	Normal	Elevated
Gram stain	+	–	–
Cytology	–	–	+

overwhelming infection [5]. If meningitis is diagnosed in the presence of these factors and diagnostic uncertainty remains about the likely cause, patients may require admission to the hospital for observation and treatment with empirical antibiotics while awaiting CSF cultures, blood cultures and other confirmatory testing. In the past, repeat LP was often performed when the diagnosis was unclear and to document sterilization of the CSF, but now repeat LP is typically only performed during specific conditions, such as in patients who are not improving despite empirical antibiotic therapy [71]. Once meningitis is demonstrated on initial CSF testing, other laboratory testing may be appropriate to further investigate the possible causes. Latex agglutination antigen testing can be used to identify bacterial pathogens in the CSF, although a wide range of reported sensitivities (50–100%) suggest that a negative result should not be used to completely exclude the diagnosis of bacterial meningitis [72]. When viral meningitis is suspected, testing for viruses by viral culture or PCR can be done. As the most common cause of viral meningitis, enteroviruses can be detected via this method, which can assist with disposition decisions and possibly decrease the unnecessary use of antibiotics [20]. Fungal pathogens can also be identified using India ink staining, fungal cultures and antigen testing. If leptomeningeal meningitis is a possibility, the CSF can also be sent for cytology [5].

CSF lactate levels have recently been proposed as a reliable marker that can help differentiate bacterial meningitis (CSF lactate > 6 mmol/L), from partially treated meningitis (CSF lactate 4–6 mmol/L) and aseptic meningitis (CSF lactate < 2 mmol/L) [73]. Although cost-effectiveness has not yet been addressed, some authors report that the CSF lactate concentration may be a good candidate as a potential single indicator to help differentiate bacterial meningitis from aseptic meningitis [73].

Other Diagnostic Studies

In patients who are diagnosed with meningitis, other laboratory studies that can be considered during an initial workup include a complete blood count (CBC), serum glucose and electrolytes, blood urea nitrogen (BUN) and creatinine, blood cultures and C-reactive protein (CRP). CRP is an acute-phase reactant that has been used as a non-specific marker of inflammation, and some studies demonstrate its elevation in patients with meningitis; however, its role in the diagnostic process remains unclear [20]. In patients with meningitis, the serum white blood cell count is commonly elevated, with a predominance of neutrophils. However, these are non-specific findings and may not apply to patients at the extremes of age and those who are immunocompromised [5]. It may be helpful to assess BUN and creatinine levels as indicators of renal function, and other laboratory testing can identify electrolyte abnormalities. Serum glucose testing may be helpful for comparison with the CSF glucose levels. Blood cultures have been shown to reveal the causative pathogen for bacterial meningitis even in cases when the CSF cultures are negative, making this a potentially useful laboratory test when bacterial meningitis is diagnosed [74].

Therapy

Empirical Antibiotics

When bacterial meningitis is considered a likely diagnosis, empirical antibiotics are indicated to begin treatment until confirmatory data and pathogen identification are available. Bacterial meningitis is an infection in an area of impaired host resistance, and, therefore, bacterial multiplication rapidly occurs (to concentrations of ten million or more colony-forming units per mL of CSF fluid) [1, 75]. In the acute care setting, the pathogen is usually unknown at the time of initial diagnosis, and, therefore, empirical coverage is recommended until bacterial identification is made [1, 13, 15, 72, 76]. Optimal antibiotic treatment requires that the drug have a bactericidal effect in the CSF, and studies have shown that patients with pneumococcal and Gram-negative meningitis who are treated with bacteriostatic agents do poorly [77]. It is important to provide coverage for the most common pathogens, including *N. meningitidis* and *S. pneumoniae*, and, therefore, a third-generation cephalosporin, such as ceftriaxone or cefotaxime, is a good first choice [20, 78]. Vancomycin should also be added to cover for resistant *S. pneumoniae* strains, as studies have shown that resistance or intermediate sensitivity rates can be as high as 3% in adults and 9% in children [79, 80]. There are certain subsets of patients in whom ampicillin should also be considered to cover for *L. monocytogenes*. These include patients who are immunocompromised, pregnant, neonates, >50 years of age and those who are alcoholics [14, 15, 76, 77, 81, 82]. If a patient has a penicillin allergy, chloramphenicol can be used as an alternative for a third-generation cephalosporin, and trimethoprim/sulphamethoxazole can be used in place of ampicillin to cover for *L. monocytogenes*. For patients who develop meningitis after penetrating head trauma or post-neurosurgery, vancomycin plus cefepime, ceftazidime and meropenem are recommended [83]. For adults who develop meningitis after a basilar skull fracture, vancomycin and a third-generation cephalosporin (i.e. ceftriaxone or cefotaxime) are recommended [83]. (See Table 14.3 for recommended empirical therapy for adults with suspected bacterial meningitis and Table 14.4 for a listing of adverse drug reactions and special considerations when choosing antibiotic therapy.)

While many references list time-based goals for antibiotic administration in cases of suspected meningitis, these arbitrary timing recommendations do not accurately reflect the current information on this topic. There are insufficient data to outline exactly the timeline of when the first dose of antibiotics should be administered to impact patient outcomes, but several retrospective studies have demonstrated that delays longer than 6 h are associated with worse outcomes [9, 12] and one prospective study of pneumococcal meningitis in the ICU found that a delay longer than 3 h was associated with a worse outcome [84]. A recent retrospective analysis suggested a lower mortality rate and decreased risk of sequelae at follow-up when patients were treated with antibiotics in less than 2 h from presentation in their cohort [67]. While prompt treatment with empirical antibiotics is recommended when meningitis is suspected, future studies may provide more robust

Table 14.3 Recommended empirical therapy for adults with suspected bacterial meningitis [5, 15, 20, 30, 72, 76, 81, 83]

Age of the patient	Intravenous empirical therapy ^a
Adults younger than 50 years	<ul style="list-style-type: none"> Dexamethasone, 10 mg given every 6 h for 4 days (initiate before or with first dose of antibiotics) Ceftriaxone, 4 g/day divided every 12–24 h, or cefotaxime 8–12 g/day divided every 4–6 h Vancomycin, 30–45 mg/kg divided every 8–12 h
Adults 50 years and older	<ul style="list-style-type: none"> Dexamethasone, 10 mg given every 6 h for 4 days (initiate before or with first dose of antibiotics) Vancomycin, 30–45 mg/kg divided every 8–12 h Ampicillin, 12 g/day divided every 4 h Ceftriaxone, 4 g/day divided every 12–24 h or cefotaxime 8–12 g/day divided every 4–6 h
Immunocompromised state	<ul style="list-style-type: none"> Vancomycin, 30–45 mg/kg divided every 8–12 h Ampicillin, 12 g/day divided every 4 h Cefepime, 2 g every 8 h, or meropenem 2 g every 8 h
Post-neurosurgery or after penetrating head trauma	<ul style="list-style-type: none"> Vancomycin, 30–45 mg/kg divided every 8–12 h Ceftazidime (2 g every 8 h) or cefepime (2 g every 8 h) or meropenem (2 g every 8 h)
Basilar skull fracture	<ul style="list-style-type: none"> Vancomycin, 30–45 mg/kg divided every 8–12 h Ceftriaxone, 4 g/day divided every 12–24 h or cefotaxime 8–12 g/day divided every 4–6 h

^aDosing for alternative antibiotics discussed in text: chloramphenicol, 4–6 g/day divided every 6 h—higher dose recommended for patients with pneumococcal meningitis; trimethoprim/sulphamethoxazole, 10–20 mg/kg/day divided every 6–12 h (dosing based on trimethoprim component) [77]

guidance to clinicians regarding optimal treatment timing when the diagnosis is made in acute care settings.

Observational studies in clinical practice have found that the average treatment time to initiate antibiotics in routine clinical practice is between 2 and 5 h after presentation [11, 85–87], which takes into account the time required for diagnostic evaluation and consideration of other diagnostic possibilities and other aspects of the patient care process. Withholding antibiotics while awaiting CT scans, laboratory data or admission will increase the time to antibiotic initiation [12, 86], and therefore, one should not delay empirical administration when bacterial meningitis is thought to be the likely diagnosis. Given that the majority of cases of bacterial meningitis were fatal before modern antibiotics, it is clear that an extended delay will lead to worse outcomes. Consequently, when bacterial meningitis is a likely diagnosis, antibiotics should be given immediately after a prompt LP, or in the instance of a delayed LP (e.g. secondary to CT scan or prolonged patient transport), antibiotics should be initiated soon after blood cultures are drawn.

Though a detailed discussion of encephalitis is out of the scope of this chapter (see Chap. 4 on ‘Coma and encephalopathy’), clinicians should consider the diagnosis of viral encephalitis in patients who, along with signs and symptoms of meningitis, also have an altered mental status or focal neurological deficits. Encephalitis

Table 14.4 Adverse drug reactions of antibiotics and special considerations

Antibiotic	Adverse drug reactions ^a	Special considerations	Renal dosing
Ampicillin	Nausea, diarrhoea, vomiting, headache, candidiasis, eosinophilia, urticaria, rash, dizziness Rare but serious (<1%): thrombocytopenia, seizures, agranulocytosis, Stevens–Johnson syndrome, interstitial nephritis, haemolytic anaemia	Pregnancy Category B Use caution if there are hypersensitivity to beta-lactams, renal impairment, history of pseudomembranous colitis, history of ALL (increased risk of rash) Lowers seizure threshold	CrCl 10–50: give q 6–12 h; CrCl <10: give q 12–24 h; HD: give dose after dialysis
Cefotaxime	Rash, pruritus, fever, eosinophilia Rare but serious (<1%): Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, thrombocytopenia, anaemia, seizures, <i>Clostridium difficile</i> -associated diarrhoea, interstitial nephritis	Pregnancy Category B Use caution if there are hypersensitivity to PCN, renal impairment, history of <i>C. difficile</i> colitis, seizure disorder, concurrent use of nephrotoxic drugs	CrCl <20: decrease dose to 50%
Ceftriaxone	Eosinophilia, thrombocytosis, elevated liver transaminases, diarrhoea, leucopenia Rare but serious (<1%): Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, serum sickness, <i>Clostridium difficile</i> -associated diarrhoea	Pregnancy Category B Use caution if there are hypersensitivity to PCN, hyperbilirubinaemia (neonates <28 days), hepatic or renal impairment; vitamin K deficiency	Renal failure: no initial adjustment, monitor serum levels; hepatic impairment with significant renal impairment: max 2 g/day unless closely monitoring the levels; HD: give dose after dialysis
Cefepime	Rash, diarrhoea, hypophosphatemia, elevated liver transaminases, nausea Rare but serious (<1%): anaphylaxis, seizures, Stevens–Johnson syndrome, leucopenia, E. multiforme	Pregnancy Category B Use caution if there is hypersensitivity to PCN; monitor BUN; Cr if elderly or renal impairment; monitor PT if there are renal or hepatic impairment, cancer, malnutrition, long-term antimicrobial tx or anticoagulant tx	CrCl 30–60: give q24h; CrCl 11–29: give usual dose × 1, then 0.5–1 g q24h; CrCl <11: give usual dose × 1, then 250–500 mg q24h; HD: 1 g × 1, then 500 mg q24h, give after dialysis; PD: give usual dose q48h

Table 14.4 (continued)

Antibiotic	Adverse drug reactions ^a	Special considerations	Renal dosing
Chloramphenicol	Nausea, vomiting, diarrhoea, headache, fever, rash, pruritus, peripheral neuropathy, optic neuritis, blurred vision Rare but serious (<1%): aplastic anaemia, hypoplastic anaemia, agranulocytosis, thrombocytopenia, pseudomembranous colitis, grey baby syndrome	Pregnancy Category C Use caution in G6PD deficiency, pregnancy, infants, hepatic or renal impairment, use of bone marrow suppressants, haematological disorder	CrCl 10–50: decrease dose to 75%; CrCl <10: decrease dose to 50%
Meropenem	Diarrhoea, nausea, vomiting, headache, rash, paraesthesia Rare but serious (<1%): seizures, anaphylaxis, Stevens–Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, <i>C. difficile</i> -associated diarrhoea, thrombocytopenia, agranulocytosis, anaemia, neutropenia, leucopenia, haemolytic anaemia	Hypersensitivity to drug class; anaphylaxis to beta-lactams; caution if there is seizure disorder or recent antibiotic-associated colitis	CrCl 26–50: give q12h; CrCl 10–25: decr. Dose 50%, give q12h; CrCl <10: decr. Dose 50%, give q24h; HD: give dose after dialysis; PD: no supplement
Trimethoprim/ sulphamethoxazole	Nausea, vomiting, urticaria, diarrhoea, GI upset, headache, lethargy, rash, anorexia, photosensitivity Rare but serious (<1%): Stevens–Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis/hepatotoxicity	Pregnancy Category C Use caution in G6PD deficiency, infants, hepatic impairment; renal impairment, concurrent anticonvulsant use, bone marrow suppressant use	CrCl 15–30: decrease dose to 50%; CrCl <15: avoid use
Vancomycin	‘Red man syndrome’ = erythematous rash on face and upper body—infusion rate-related, chills, hypotension (infusion rate-related), rash, eosinophilia, reversible neutropenia, elevated BUN/creatinine levels, fever, rash, chills, vertigo Rare but serious (<1%): tissue necrosis with extravasation, interstitial nephritis, thrombophlebitis, Stevens–Johnson syndrome, toxic epidermal necrolysis	Pregnancy Category C Avoid rapid i.v. infusion; dose accordingly for renal-impaired patients; use caution with concurrent use of nephrotoxic agents or ototoxic agents	CrCl >50: 15 mg/kg × 1, then usual dose q 12–24 h; CrCl 10–50: 15 mg/kg × 1, then usual dose q 24–96 h; CrCl <10: 15 mg/kg × 1, then usual dose q 4–7 days

Data obtained from Epocrates Online database, <https://online.epocrates.com/> accessed on May 13, 2015

Note that all of these antibiotics can cause anaphylactic/anaphylactoid reactions though these are rare (<1%) for each antibiotic

CrCl creatinine clearance, HD haemodialysis, ALL acute lymphoblastic leukaemia, PCN penicillin, G6Pd glucose-6-phosphate dehydrogenase

^aIncluded are the more common drug reactions that occur in 1–10% of patients (unless otherwise noted)

is caused by a variety of pathogens, and there is no specific treatment other than supportive care, except if the pathogen is HSV, when treatment with acyclovir is appropriate [15]. In patients with altered mental status and focal neurological deficits where encephalitis is a concern, clinicians should consider administering empirical acyclovir in addition to empirical antibiotic therapy. Studies have shown that a majority of patients ultimately diagnosed with encephalitis do not receive acyclovir in the emergency department, despite a clinical presentation suggestive of encephalitis, which may highlight some of the challenges in diagnosing and treating this uncommon condition [88].

Corticosteroids

Bacterial meningitis is associated with an inflammatory response in the subarachnoid space, which experimental studies have shown to be poorly tolerated [71]. Meningitis can lead to CNS inflammation and can produce raised intracranial pressure, glial scarring, seizures and permanent neurological sequelae [30]. Adjunctive use of corticosteroids has been shown to decrease this inflammatory response and proposed as an adjunctive therapy in addition to empirical antibiotics in the treatment of bacterial meningitis [77, 82, 89–91]. Children with bacterial meningitis caused by *H. influenzae* have a decreased risk of hearing loss if a corticosteroid is used [1, 90]. One prospective, randomized, double-blind multicentre trial of 301 patients showed that the use of dexamethasone before or with the first dose of antibiotic, continued every 6 h for 4 days, was associated with improved patient outcomes [92]. Studies have also shown that the use of corticosteroids is not associated with an increased risk of gastrointestinal bleeding, fungal infections, fever or herpes infections [91–93].

The recent Cochrane Database review of 4121 adults and children from a number of randomized trials demonstrated a reduction in hearing loss and other neurological sequelae in participants in high-income countries who have bacterial meningitis; however no effect was found in low-income countries [90]. Subgroup analysis suggests that patients with meningitis due to *S. pneumoniae* treated with corticosteroids had a lower death rate, while no effect on mortality was seen in patients with *H. influenza* and *N. meningitidis* [90]. Dexamethasone increased the rate of recurrent fever but was not associated with other adverse events [90]. Several studies from developing countries have led to some controversy about the use of steroids in children from these areas, and it is unclear at this time whether adjunctive steroids are beneficial in this specific population, the matter being complicated by high rates of HIV infection and issues of access to care [91, 94].

When steroids are given, the recommended dose of dexamethasone for adults is 10 mg and for children, 0.15 mg/kg intravenously every 6 h for 4 days, with the first dose administered before or with the first dose of antibiotics [5, 72]. It is important to remember that the first dose of adjunctive treatment with corticosteroids should be given before or with the first dose of antibiotics. Dexamethasone inhibits the release of interleukin (IL)-1, tumour necrosis factor (TNF) and other inflammatory cytokines which are released by microglia and macrophages when activated by

endotoxins released from the killing of bacteria and appears to have a limited effect after this inflammatory cascade has commenced [5, 95, 96].

Disposition

Patients diagnosed with bacterial meningitis should be admitted to the hospital for monitoring and administration of intravenous antibiotics and consideration of other adjunctive treatments. There can be some clinical ambiguity regarding disposition for patients who have mildly elevated CSF white blood cells but appear well and have other findings indicative of a likely aseptic viral meningitis. The options for treating these patients include hospital admission for observation, with or without empirical antibiotic therapy pending CSF culture results. Outpatient management with close follow-up and a discussion of reporting back in case of appearance of new symptoms or worsening of prevailing ones may be appropriate for some patients with diagnosed viral meningitis. When considering discharge for outpatient management of presumed viral meningitis, it is important to consider a patient's support system and reliability, the availability of close follow-up and mechanisms for contacting the patient if the results of CSF culture are unexpectedly positive [20].

Complications of Bacterial Meningitis

Despite advances in antibiotics, vaccines and adjunctive treatments, patients with bacterial meningitis continue to suffer significant morbidity and mortality. Complications can be devastating and can be divided into systemic and neurologic categories. Systemic complications are often related to the bacteremia that frequently occurs with meningitis and can include sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation and septic or reactive arthritis [15, 62]. Neurologic complications include impaired mental status, sensorineuronal hearing loss, seizures, focal neurologic deficits such as cranial nerve palsy or hemiparesis and intellectual impairment. These complications may be sudden or gradual in onset and can even develop after completion of therapy. Often hearing loss can be subtle and may not be detected in the early phase of infection [62]. See Table 14.5 for a listing of complications related to meningitis. See Fig. 14.1 for illustrations of meningitis-associated cerebral infarct and cerebral oedema.

Table 14.5 Complications of bacterial meningitis [15, 62]

Systemic complications	Neurologic complications
Death	Impaired mental status
Bacteremia	Sensorineuronal hearing loss
Acute respiratory distress syndrome	Focal neurologic deficits such as cranial nerve palsy or hemiparesis
Septic shock	Seizures
Septic or reactive arthritis	Intellectual impairment
Disseminated intravascular coagulation	Increased intracranial pressure and cerebral oedema
Bacteremia	Cerebrovascular abnormalities

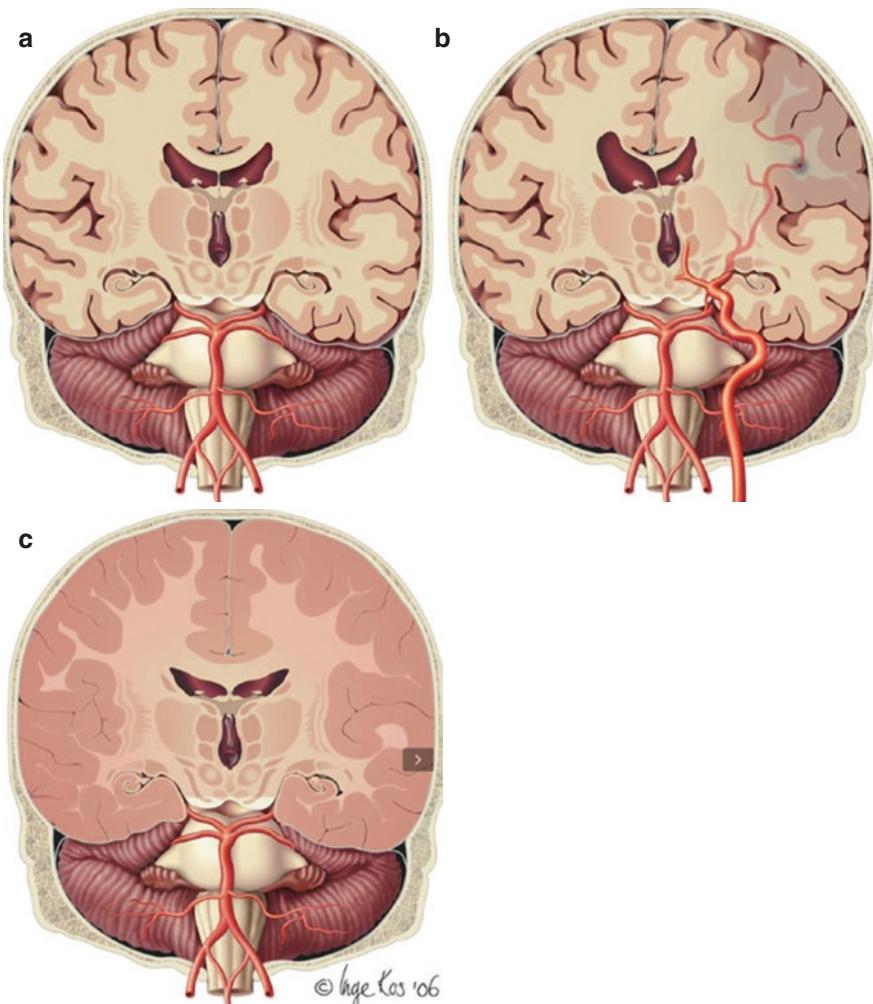


Fig. 14.1 (a) Normal brain, (b) meningitis-associated cerebral infarct causing pronounced brain shift which can lead to focal neurologic deficits and (c) cerebral oedema associated with meningitis. Reprinted from Lancet Infectious Diseases, Volume 7, Michael T. Fitch and Diederick Van de Beek, Emergency diagnosis and treatment of adult meningitis, pages 191–200, Copyright 2007, with permission from Elsevier

Prognosis

It is important to appropriately risk-stratify patients diagnosed with bacterial meningitis as many may require an intensive care unit or a high-dependency setting [20]. The prognosis depends on factors such as age, the presence of co-morbidities, severity of the illness and the neurological examination at presentation [95, 97]. The

most important factors contributing to an unfavourable outcome include tachycardia, hypotension, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopenia, low CSF leucocyte count, altered mental status, seizure within 24 h of admission, need for mechanical ventilation, signs of increased intracranial pressure and likely *S. pneumoniae* infection (advanced age, presence of otitis or sinusitis or pneumonia, immunosuppression) [5, 14, 20, 95, 98].

Before the routine use of the pneumococcal conjugate vaccine, the annual mortality rate in the USA for bacterial meningitis was about 6000, with two-thirds of all cases occurring in children [1]. In 2003, the rate had come down to 708 [99]. Although the overall incidence appears to be decreasing in children, the proportion in the elderly population is actually increasing [18, 100]. This trend could be due to the widespread use of vaccines, as well as to an ageing population with increased co-morbidities [5]. Currently, the case fatality rates are 4–10% for children [59], 13–27% for adults [6–13] and up to 50% for the elderly [100]. Case fatality rates appear to differ depending on the causative pathogen and the patient's age.

Conclusion

The diagnosis of meningitis can be very challenging, and clinicians must combine the findings of the history, physical examination and laboratory investigations to accurately diagnose the condition. Clinicians may find an algorithmic approach to diagnosis and treatment useful as a starting point when approaching patients with a high likelihood of bacterial meningitis (see published algorithm in references 14 and 15). While many causes of meningitis, such as viral infection or rheumatological disease, typically have a benign clinical course, bacterial meningitis can be life-threatening. Despite advances in medical care which include the development of vaccines, antibiotics and adjunctive therapies, bacterial meningitis continues to have a significant morbidity and mortality rate even when patients are treated appropriately. Ongoing research, combined with continuing efforts to improve diagnostic abilities, will lead to improved methods of diagnosing and treating potentially life-threatening infections of the CNS.

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Viral Encephalitides

15

Heng Thay Chong and Chong Tin Tan

Introduction

Viral encephalitis is defined as an inflammation of the brain parenchyma caused by viral infection. There is often concomitant involvement of the surrounding meninges, a condition generally referred to as meningoencephalitis. This chapter focuses on viral encephalitis as viral meningitis is dealt with in Chap. 14. Other non-infective causes include autoimmune encephalitis and Rasmussen syndrome. The pathological findings in most encephalitides are non-specific and include neuronal death, perivascular cuffing, mononuclear cell infiltration and, later, gliosis. In herpes encephalitis, homogeneous, eosinophilic intranuclear inclusion bodies (Cowdry type A) are seen in about half of the patients in the first week of infection. After about 2 weeks, gliosis, glial nodule and satellitosis–neuronophagia with necrosis and haemorrhage are seen. In rabies infection, intracytoplasmic inclusion or Negri bodies are seen in 80% of patients. In less common infections, the pathological process may differ. In acute Venezuelan equine, Eastern equine and Nipah and Hendra encephalitides, there is widespread vasculitis, thrombosis and infarction, while demyelinating encephalitis is seen in herpes simplex encephalitis in the immunocompromised and in human herpesvirus 6 (HHV6) infections [1–5].

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Incidence

The annual incidence of viral encephalitis in developed countries is 1–7.4/100,000. It is higher among children, and, in those of the age of 1–2 years, it is 16.7/100,000 per annum. In developing and resource-constrained countries, the incidence and prevalence are less well studied and depend on the local infection pattern. In Northern Thailand, for example, where Japanese encephalitis (JE) is endemic, the incidence of viral encephalitis is as high as 40/100,000 for those between 5 and 25 years old, and JE accounts for 20–30% of all cases with a diagnosis of viral encephalitides [6–8].

Causes

Both the differential diagnoses and causes of viral encephalitides are many. The viruses that cause human CNS infection can be divided into primary human viruses, zoonotic and arthropod-borne viruses or arboviruses. Apart from the herpesviruses, paramyxoviruses, adenovirus and JC virus, which are DNA viruses, most of the other viruses are RNA viruses. While all the primary human viruses have a worldwide distribution, most of the arboviruses, though not worldwide in distribution, affect large parts of the continents and are spreading rapidly across borders. The zoonotic viruses, on the other hand, generally have more limited distribution, except for rabies virus and B virus (Table 15.1). However, in many countries, only

Table 15.1 Viruses that affect the human central nervous system in different regions

Region	Virus
Worldwide	Herpesviruses (HSV1 and 2, VZV, EBV, CMV and HHV6), enteroviruses, mumps, measles, rubella, HIV, adenovirus, parvovirus B19 and JC virus, rabies virus and B virus (Herpes simiae or Cercopithecine herpesvirus 1)
Asia, Africa, Australia, Central and South America	Dengue virus
East and Southeast Asia	Japanese encephalitis virus, Nipah virus, Kunjin virus, Negishi virus (Japan), Powassan virus (Eastern Russia), Tahyna virus (Northwest China)
South Asia	Japanese encephalitis virus, West Nile virus, Kyasanur forest virus (India), Nipah virus
Middle East	West Nile virus, Alkhurma virus (Arab peninsula), Rift Valley encephalitis virus (southwest corner of Arab peninsula)
Africa	West Nile virus, Rift Valley fever virus, Lassa fever virus, Marburg virus, Ebola virus, Mokola virus
Western Europe	West Nile virus (south), louping ill virus (British isles), Toscana virus (Spain and Italy), lymphocytic choriomeningitis virus, Western European tick-borne encephalitis virus
Eastern Europe	West Nile virus, Tahyna virus, Inkoo virus, Omsk haemorrhagic fever virus, Far Eastern and Siberian tick-borne encephalitis virus, snowshoe hare virus and Powassan virus

Table 15.1 (continued)

Region	Virus
North America	West Nile virus, St. Louis virus, California encephalitis (including LaCrosse virus), Western equine encephalitis virus, Eastern equine encephalitis virus, Jamestown Canyon virus, Colorado tick fever virus, snowshoe hare virus, Powassan virus
Central and South America	Venezuelan equine encephalitis virus, Ilheus virus, Machupo virus, Guanarito virus, Rocio virus, Junin virus, Sabia virus, Hantavirus (Andes virus)
Australia	Murray Valley encephalitis virus, Kunjin virus, bat lyssavirus, Hendra virus

HSV herpes simplex virus, *VZV* varicella zoster virus, *EBV* Epstein–Barr virus, *CMV* cytomegalovirus, *HHV* human herpesvirus, *HIV* human immunodeficiency virus

Table 15.2 Differential diagnoses of viral encephalitis

<i>Non-infective causes</i>	
Autoimmune diseases	Acute disseminated encephalomyelitis, CNS vasculitides, autoimmune encephalitis, Rasmussen syndrome, cerebral lupus, Bickerstaff encephalitis
Metabolic syndromes	Acute diabetic complications, thyrotoxic storm, thrombotic thrombocytopenic purpura, hepatic encephalopathy, uraemic encephalopathy, mitochondrial disease, Wernicke encephalopathy, serotonin syndrome, neuroleptic malignant syndrome, Wilson disease
Other systemic diseases	CNS lymphoma, malignant hypertension, non-convulsive status epilepticus, sagittal sinus thrombosis, hypoxic encephalopathy, acute poisoning (organophosphate, lead)
<i>Infective causes</i>	
Bacterial	Cerebral abscess, actinomycoses, <i>Bartonella henselae</i> (cat-scratch disease), <i>Borrelia burgdorferi</i> , brucellosis, legionellosis, leptospirosis, <i>Listeria monocytogenes</i> , tuberculous meningitis, <i>Mycoplasma pneumoniae</i> , nocardiosis, typhoid, syphilis, <i>Tropheryma whipplei</i> (Whipple disease)
Rickettsial	Ehrlichiosis, Q fever, Rocky Mountain spotted fever
Fungal	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis
Parasitic	Cerebral malaria, <i>Naegleria fowleri</i> , toxoplasmosis, trypanosomiasis, schistosomiasis

Adapted and modified from Kennedy PGE. Viral encephalitis. *J Neurol* 2005;252:268–72, and Chaudhuri A, Kennedy PGE. Diagnosis and treatment of viral encephalitis. *Postgrad Med J* 2002;78:575–83

15–70% of clinical viral encephalitis patients have a definitive microbiological diagnosis even with advanced laboratory investigation, such as serology, polymerase chain reaction (PCR) and viral culture [9–11]. The main differential diagnoses include other infections, autoimmune diseases and metabolic diseases (Table 15.2).

Clinical Features

The cardinal features of viral encephalitis are fever, headache and focal and/or diffuse neurological deficits. Other clinical features include meningism, personality changes, psychosis, behavioural changes, drowsiness, seizures, confusion and respiratory and abdominal symptoms, such as nausea and vomiting. However, it is not easy to differentiate acute viral encephalitides from other conditions. An acute presentation of fever and confusion may occur in many diseases, ranging from bacterial, rickettsial, fungal, tuberculous and parasitic infections to metabolic and autoimmune conditions of the central nervous system. The diagnosis of viral encephalitis should be based on positive features and should not be made by exclusion. Other diagnoses should be considered as many, if not all, of these can be effectively treated (Table 15.2) [12].

In ascertaining the aetiology of viral encephalitis, the history of exposure is important. As many viruses have limited geographical distribution, a knowledge of the local viral infection patterns, a history of if and where the patient has travelled and whether he has come in contact with animals or received any insect bites are useful clues to the diagnosis (Tables 15.2 and 15.3). Certain viruses may affect a particular segment of the population more than another or present with specific clinical features not seen in many other viral encephalitides. Japanese encephalitis

Table 15.3 Hosts, reservoirs and vectors of viruses that affect the human central nervous system

Primary human viruses		Host/ reservoir/ vector(s)
Herpesviruses	Herpes simplex virus 1 and 2, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, human herpesvirus 6	<i>Human</i>
Enteroviruses	Poliovirus 1–3; Coxsackie virus A1–22, 24, B1–6; echovirus 1–7, 9, 11–27, 29–33; enterovirus 68–71	
Others	Mumps, measles, rubella, human immunodeficiency virus, human T-cell lymphoma virus, adenovirus, parvovirus B19, JC virus	
Arboviruses		
Flaviviruses (mosquito-borne)	Japanese encephalitis virus	<i>Pig—Mosquito</i>
	West Nile virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Kunjin virus, Ilheus and Rocio viruses	<i>Bird—Mosquito</i>
	Dengue	<i>Mosquito</i>
Flaviviruses (tick-borne)	Far eastern, Western European and Siberian tick-borne encephalitis viruses, Powassan virus	<i>Small mammal—Tick</i>
	Louping ill virus	<i>Sheep—Tick</i>
	Omsk haemorrhagic fever virus	<i>Muskrats—Tick</i>
	Kyasanur forest virus	<i>Mammals—Tick</i>
	Alkhurma virus	<i>Unknown—Tick</i>

Table 15.3 (continued)

Primary human viruses		Host/ reservoir/ vector(s)
Bunyaviruses	California encephalitis, LaCrosse encephalitis, Tahyna virus	<i>Mammal—Mosquito</i>
	Jamestown Canyon encephalitis virus	<i>Deer, horse—Mosquito</i>
	Snowshoe hare viruses	<i>Snowshoe hare, squirrel—Mosquito</i>
	Inkoo virus	<i>Unknown—Mosquito</i>
	Rift Valley encephalitis virus	<i>Ruminants—Mosquito</i>
	Toscana virus	<i>Sandfly</i>
Togaviruses	Western equine and Venezuelan equine encephalitis viruses	<i>Horse—Mosquito</i>
	Eastern equine encephalitis virus	<i>Horse, bird, small mammal—Mosquito</i>
Reovirus	Colorado tick fever virus	<i>Tick</i>
Zoonotic viruses		
Rhabdovirus	Rabies	<i>Dog, small mammal</i>
	Bat lyssavirus	<i>Bat</i>
	Mokola virus	<i>Small mammal</i>
Herpesvirus	B virus (Herpes simiae or Cercopithecine herpesvirus 1)	<i>Monkey</i>
Filoviruses	Marburg and Ebola viruses	<i>Bat, monkey</i>
Paramyxoviruses	Nipah virus	<i>Bat, pig</i>
	Hendra virus	<i>Bat, horse</i>
Arenaviruses	Lymphocytic choriomeningitis virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus, Sabia virus	<i>Rodent</i>
Bunyavirus	Hantaviruses (Puumala and Andes viruses)	<i>Rodent</i>

virus, LaCrosse virus, Tahyna virus, enteroviruses and adenoviruses are more likely to affect children than adults, while West Nile virus and the alphaviruses affect the elderly more commonly. Zoonotic and tick-borne viruses tend to affect males more than females because the former are more likely to be involved in outdoor activities and animal husbandry. Some viruses, such as cytomegalovirus and JC virus, have a predilection for immunosuppressed hosts, while others, such as measles inclusion body encephalitis and recurrent enteroviral encephalitis or meningitis, produce different clinical manifestations among immunosuppressed and immunocompetent hosts. Tick-borne encephalitis, including louping ill virus encephalitis, and Kyasanur forest viral encephalitis are typically biphasic in presentation, while Nipah and Hendra viruses may cause relapses of encephalitis. In the case of Nipah virus, relapses can be seen even up to years after the initial infection. Nipah encephalitis, Japanese encephalitis, St. Louis encephalitis and rabies are known to cause myoclonus and/or opsoclonus. Some viruses may affect other parts of the CNS, besides the cerebrum, or have significant associated systemic features (Table 15.4) [13].

Table 15.4 Specific clinical features of some viral encephalitides

Specific clinical features	Viruses
Neurological	
Myoclonus/opsoclonus	Nipah, Japanese encephalitis, West Nile
Parkinsonism	Japanese encephalitis, West Nile, Western equine encephalitis, tick-borne encephalitis
Cerebellar involvement	Varicella zoster, Junin
Brain stem involvement	St. Louis encephalitis, West Nile, tick-borne encephalitis, enterovirus 71
Autonomic involvement	Herpes simplex, Nipah, furious rabies
Spinal cord involvement	Japanese encephalitis, West Nile, paralytic rabies, tick-borne encephalitis, CMV, HIV, HTLV-1
Systemic	
Hepatic and/ or renal failure	Rift Valley fever, Hantavirus (Puumala virus)
Respiratory and gastrointestinal symptoms	LaCrosse, Venezuelan equine encephalitis, Guanarito, Nipah, Hantavirus (Andes virus)
Haemorrhage	Lassa, Junin, Machupo, Guanarito, Sabia, Marburg, Ebola, Omsk haemorrhagic fever, Alkhurma, Kyasanur forest, Rift Valley fever, Dengue, Hantavirus (Puumala virus)
Urinary symptoms	St. Louis encephalitis

CMV cytomegalovirus, *HIV* human immunodeficiency virus, *HTLV-1* human T-cell lymphoma virus type 1

Investigations (Tables 15.5, 15.6 and 15.7)

Blood Tests and Chest X-Ray

Simple laboratory investigations are not specific but may be useful in differentiating viral encephalitis from other illnesses (Table 15.5). Peripheral blood film examination may reveal malaria parasites within erythrocytes, monocytic cytoplasmic inclusion body in human ehrlichiosis or intravascular haemolysis in thrombotic thrombocytopenic purpura. Abnormal liver and/or renal function tests may indicate leptospirosis, Wilson disease, electrolyte disturbances and hepatic or uraemic encephalopathy. Thyroid function test and thyroid antibodies are essential for the diagnosis of thyrotoxic storm or Hashimoto encephalopathy, and blood sugar level should be estimated in those with acute diabetic complications. A simple chest X-ray may reveal that tuberculosis, fungal infection or atypical pneumonia is the cause of the presentation instead of viral encephalitis [12, 37]. More specific tests, such as autoantibodies for autoimmune encephalitis, are indicated if the clinical features raise suspicion of these conditions.

Table 15.5 Laboratory investigations in patients with suspected viral encephalitis

Modality	Investigations
Blood	Peripheral blood film examination, random blood sugar, liver function test, renal function test (urea, electrolytes and creatinine), thyroid function test, serology and autoantibodies study (e.g. lupus, autoantibodies for autoimmune encephalitis, paraneoplastic syndromes, Hashimoto encephalopathy, etc.)
Cerebrospinal fluid	Microscopic examination, biochemical analysis, bacterial and mycobacterial staining and culture, cryptococcal antigen study, viral-specific IgM test, nucleic acid amplification test (e.g. PCR), viral culture
Radioimaging	MRI, angiogram (vasculitides), CT scan if MRI is contraindicated
Neuroelectrophysiology	Electroencephalogram
Histopathology	Nape of neck skin biopsy and sensory neuron antibody study (rabies), brain biopsy

Table 15.6 Viral encephalitides and magnetic resonance imaging findings

Encephalitis	MRI changes
Herpes simplex [14, 15]	T ₁ W hypointense and T ₂ W hyperintense lesions in inferomedial temporal lobe, superficial temporal lobe, external capsule, insular cortex, rectus gyrus, brain stem, frontal lobe, basal ganglia, periventricular white matter. Mass effect in a minority of patients. Bitemporal involvement is nearly pathognomonic
Human herpesvirus 6 [14, 16]	T ₂ W hyperintensities in frontal, temporal and/or parietal white matter; temporal lobe and limbic system oedema and limbic encephalitis
Cytomegalovirus [17, 18]	<i>Acute encephalitis:</i> Ependymal and periventricular subependymal contrast enhancement, subependymal ring-enhanced lesions, ventricular dilatation and periventricular white matter atrophy. In diffuse disease, widespread basal ganglia, hippocampal, cerebellar and brain stem T ₂ W hyperintense nodular lesions, some with rim enhancement on T ₁ W contrast images. Occasional haemorrhages and/or mass lesion with marked oedema <i>Polyradiculomyelitis:</i> Thickened cauda equina which enhances diffusely, with enhancement of the leptomeninges, dorsal root and conus medullaris <i>Congenital:</i> Intracranial calcifications, ventricular dilatation, T ₂ W image hyperintensities in white matter, haemorrhage, cerebellar hypoplasia, hydrocephalus, migration disorders (polymicrogyria and/or schizencephaly)
Epstein–Barr virus[14]	T ₂ W hyperintensities in cortical grey and white matter and spinal cord
Varicella zoster [14, 19]	Large vessel arteritis and ischaemia, haemorrhagic infarcts; smaller infarcts with demyelination lesions. Homogeneous periventricular enhancement and hyperintensities <i>In immunocompromised:</i> Multiple, well-defined hemispheric white matter spherical lesions that gradually coalesce and cavitate over months. Haemorrhage and ring enhancement may occur later
Enterovirus 71 [20–22]	T ₂ W hyperintense lesions in pontine tegmentum, medulla oblongata, midbrain and cerebellar dentate nucleus. MRI abnormal in about half of patients with mild disease and in all of the patients with severe disease

(continued)

Table 15.6 (continued)

Encephalitis	MRI changes
Coxsackie B4 [23]	Bilateral T ₁ W and T ₂ W images hyperintensities in the substantia nigra
Adenovirus [24]	T ₂ W images hyperintense signal in spinal cord
Influenza [25]	Diffuse cortical and subcortical, symmetrical thalamic, cerebellar, basal ganglia and brain stem involvement
Nipah [26–28]	<i>Acute:</i> widespread focal lesions in the white matter on T ₂ W and FLAIR <i>Relapse:</i> diffuse, patchy and confluent, grey matter hyperintense T ₂ W lesions
Measles [29, 30]	<i>Subacute measles encephalitis:</i> T ₂ and FLAIR confluent hyperintense lesions in the temporal and frontal gyri, the caudate nucleus and putamen <i>Subacute sclerosing panencephalitis:</i> subcortical atrophy with T ₁ hypointense and T ₂ hyperintense lesions in the cortical and subcortical area, especially in the occipital lobes
Dengue [31, 32]	Bilateral thalamic and basal ganglia lesions, cerebral oedema or haemorrhage
West Nile [14, 31]	T ₂ W hyperintensities in basal ganglia, thalamus, substantia nigra and spinal cord and meningeal enhancement
Japanese encephalitis[14, 31]	T ₁ hypointense and T ₂ hyperintensities in basal ganglia, especially thalamus, basal ganglia, midbrain and substantia nigra
Tick-borne encephalitis [33]	Lesions in the thalamus, cerebellum, brain stem, caudate nucleus in up to 18% of patients
St. Louis encephalitis [14]	Hyperintense lesions in basal ganglia, thalamus, substantia nigra
Murray Valley encephalitis[14, 34, 35]	T ₂ hyperintensities and T ₁ hypointensities in thalamus, reticular formation, substantia nigra, red nucleus, basal ganglia, hippocampus, insular cortex, with diffusion restriction on diffusion-weighted images (DWI)
Eastern equine encephalitis [14]	Non-enhancing focal lesions in basal ganglia, thalamus and brain stem
Creutzfeldt–Jakob[14]	<i>Sporadic:</i> normal, or T ₂ or FLAIR hyperintense lesion on basal ganglia, cortical ribboning on FLAIR and DWI <i>Variant:</i> T ₂ hyperintensities on pulvinar (pathognomonic)
JC virus (PML) [14]	Multiple confluent subcortical white matter lesions on T ₂ W or FLAIR
Jamestown Canyon encephalitis [36]	Gadolinium-enhanced lesions over the cerebellar sulci, gyri, vermis and leptomeninges

Table 15.7 Viral encephalitides and cerebrospinal fluid abnormalities

Parameter	Findings
Biochemistry and cell count	Raised protein and normal glucose levels. Polymorphonuclear pleocytosis in the first 48 h; lymphocytic pleocytosis later. May be normal in immunocompromised patients and 5–25% of immunocompetent patients with viral encephalitis
Serology	Positive 7–12 days after onset of symptoms, persists for 1–3 months. False-positive in traumatic tap, cross-reaction with virus from the same family and false-negative if performed too early
Nucleic acid amplification	Positive within the first 7–10 days of the onset of symptoms. May estimate viral load. False-positive in specimen contamination and false-negative in traumatic tap or if the sample is taken too late during the course of infection

Neuroimaging Studies

Computed tomography (CT) scan of the brain is often taken before doing a lumbar puncture, though this is not always necessary. It is, however, useful to differentiate brain abscess and other space-occupying lesions from viral encephalitides. The CT scan may also delineate temporal lobe hypodense lesions with or without haemorrhage in 70% of patients with herpes simplex encephalitis. Magnetic resonance imaging (MRI) is more sensitive and useful [12, 38]. In general, the arboviruses affect the basal ganglia, thalamus, substantia nigra and brain stem, whereas the other viruses tend to affect the cerebral grey and white matter (Fig. 15.1 and Table 15.6).

Electroencephalogram

It is important to obtain an electroencephalograph (EEG) in patients with suspected viral encephalitis. It is the only definitive test for nonconvulsive status epilepticus and many subtle partial seizures that not only mimic but also complicate viral encephalitis. In herpes simplex encephalitis, the EEG may reveal periodic epileptiform discharges during the second week of illness in about half of the patients. In patients with Nipah encephalitis, independent bitemporal periodic complexes herald a poor prognosis. In subacute sclerosing panencephalitis, the EEG shows high-amplitude, periodic, sharp-and-slow wave complexes, time-locked with myoclonic

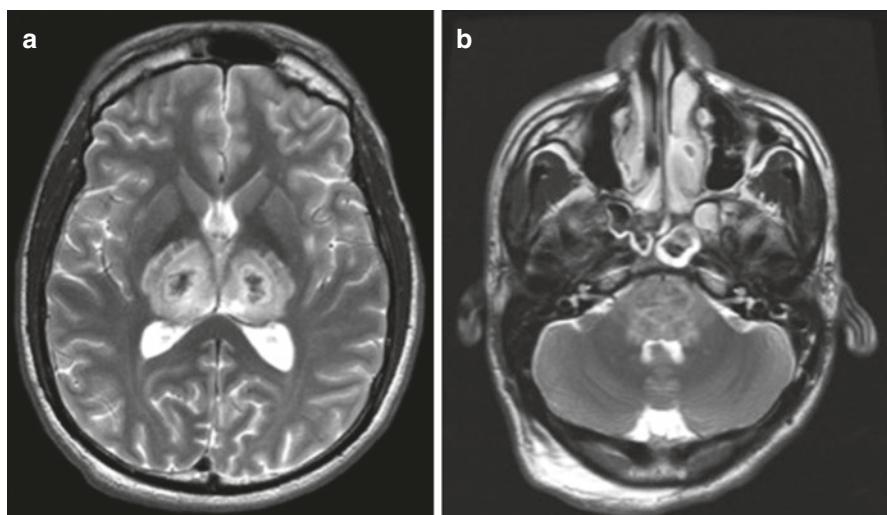


Fig. 15.1 (a, b) MRI brain axial T2-weighted image of an adult man with dengue encephalitis showing high signal lesion in both thalamus and the pons, with evidence of central haemorrhage in the thalamus. Bilateral thalamic and basal ganglia lesion is also common in Japanese encephalitis (Courtesy of Dr. Sherrini Ahmad, University of Malaya)

jerks. In most viral encephalitides, however, the EEG shows only non-specific diffuse or focal slow waves [39].

Cerebrospinal Fluid Study

Although cerebrospinal fluid (CSF) study is the single most important investigation in patients with CNS infection, lumbar puncture, as a rule, is contraindicated in the presence of raised intracranial pressure, such as within 30 min after generalized tonic–clonic seizure or in the presence of a focal mass lesion. The normal CSF contains five or less mononuclear cells per mm³ and < 0.45 g/L of protein. The presence of a single polymorphonuclear cell may be considered abnormal. A raised protein level is seen in conditions that cause capillary leakage, while a raised leucocyte count usually indicates inflammation. In traumatic lumbar puncture, 1 leucocyte is subtracted for every 800 erythrocytes/mm³; and 0.01 g/L protein is subtracted for every 1000 erythrocytes/mm³ [40]. This, however, is only an estimate based on the average leucocyte-to-erythrocyte and protein-to-erythrocyte ratios in the blood. If possible, the lumbar puncture should be repeated for a more accurate analysis. It is important to measure opening pressure, as a very high pressure raises suspicion of an alternative diagnosis, such as tuberculous or cryptococcal meningitis. The typical CSF finding in viral encephalitis is raised lymphocyte count with normal or raised protein level and normal level of glucose (Table 15.7). The total leucocyte count is usually <500/mm³. During the first 48 h of infection, there may be polymorphonuclear pleocytosis in viral encephalitis; however, the presence of a higher number of polymorphonuclear cells in the CSF beyond this may indicate bacterial infection, acute disseminated encephalomyelitis or acute haemorrhagic leucoencephalitis, *Naegleria fowleri* amoebic meningoencephalitis and enteroviral (especially echovirus 9) or Eastern equine encephalitis. Some patients with viral encephalitis have normal CSF findings, and the proportion varies according to the specific viral agent and the patient's immune status. Patients who are immunocompromised are more likely to have a normal CSF. About 5% of patients with acute herpes simplex encephalitis, 10% of patients with St. Louis encephalitis and 25% of patients with acute Nipah encephalitis have normal CSF findings. Therefore, normal CSF findings, especially in the context of a strong clinical suspicion, do not exclude the diagnosis of viral encephalitis [26, 41, 42].

Cerebrospinal Fluid Serology

CSF serology is useful in the diagnosis of most viral encephalitides, including herpes simplex, varicella zoster, and Japanese, West Nile, tick-borne, St. Louis, LaCrosse, Western equine, Eastern equine, Venezuelan equine, Nipah, Hendra, Rift Valley, Murray Valley and Kunjin encephalitis. The antibodies can be detected within 7–12 days after the onset of symptoms and persist for 1–3 months. The drawbacks of a serological test are many. A false-positive result may occur when

antibodies cross-react with antigens of other viruses from the same genus or family. For example, herpes simplex virus serology may be positive in varicella zoster virus infection and Japanese encephalitis virus in dengue or other flaviviral encephalitis. Serology, especially the single-titre IgG test, may be falsely positive in a traumatic tap CSF specimen, especially if the infection is common in the community; 60–100% of adults in the community have positive serum IgG to HSV1 and 10–80% to HSV2. The serology test may also be negative if the specimen is taken too early during the course of the illness. The other drawback of serological testing is that the results are often available relatively late—up to 10 days after the onset of symptoms. Only 50% of patients with biopsy-proven HSV encephalitis had a fourfold rise in antibody titres in the CSF. Using a serum to CSF antibody ratio of 20 or less did not improve the sensitivity of the test [40, 43]. The serological test is not practical in enteroviral infection as there are more than 60 serotypes of viruses in the genus, unless a specific serotype is suspected, such as enterovirus 71 [38].

During the first days of illness, PCR is the best aetiological diagnostic test. It has been used widely in the diagnosis of many infections, including herpes simplex and Japanese encephalitis. Apart from being highly specific and sensitive, PCR is often positive at the onset of neurological symptoms and antedates positive serological test. It can also be used to estimate the number of viral genomes in some infections to indicate the viral load in a particular infection. In herpes simplex encephalitis, for example, the sensitivity and specificity of PCR are 75–94% and 98–100%, respectively, whereas for cytomegalovirus, the sensitivity and specificity are 79% and 95%, respectively. A herpes simplex viral load of more than 100 copies of DNA/ μ l is associated with reduced consciousness, abnormal CT scan findings and poor outcome [44]. However, after 7–10 days of treatment with acyclovir, PCR often becomes negative. Therefore, herpes simplex PCR may also be falsely negative in the CSF if obtained too early or late during the course of the illness or if the specimen is contaminated with blood, as haem products inhibit PCR. PCR may also be falsely positive if the specimen is contaminated (Table 15.7) [38].

Skin Biopsy, Corneal Smear and Other Diagnostic Methods in Rabies Infection

Although the diagnosis of furious rabies is often not a problem for the experienced practitioner and investigations are often not attempted in developing countries, the diagnosis of approximately 30% of cases of paralytic rabies is difficult. The fluorescent antibody test done on a corneal smear has low sensitivity (<50%) and should not be relied upon, even though its specificity approaches 100% [45]. Repeated full-thickness biopsy of the skin from the nape of the neck, with staining of the sensory neurons using immunofluorescent antibodies, has a sensitivity of 50–94% and a specificity that approaches 100% [14]. Other tests include viral isolation from the saliva or CSF, using murine neuroblastoma cell cultures, reverse transcriptase (RT)-PCR or nucleic acid sequence-based amplification (NASBA) on tear, saliva and CSF and antibody detection tests, such as enzyme-linked immunosorbent assay

(ELISA), of serum or CSF samples [46, 47]. PCR on three serial saliva samples or three different samples (such as saliva, CSF, urine and skin) is nearly 100% sensitive in the diagnosis of early rabies. Viral excretion, however, is intermittent and is affected by circulating antibodies; therefore, serial samples are needed within the first 3–7 days, beyond which false-negative rates are high. Antibodies, on the other hand, are produced only after the first week, and antibody tests are positive only after the first week of infection. Therefore, though a positive result is indicative of rabies, a negative one does not exclude it, and repeated tests are needed [48, 49]. The diagnosis can also be established if the infecting animal is available for post-mortem direct fluorescent antibody test or histopathological examination of the brain (Table 15.8).

Table 15.8 Diagnostic tests, sensitivity and specificity

Infection	Test	Sensitivity (%)	Specificity (%)	Note
Herpes simplex virus	CSF PCR	90	~100	
Rabies virus	PCR from three different specimens	~100	~100	Specimens from either saliva, urine, CSF or hair follicle
Japanese encephalitis virus	Serum ELISA	95	95	May cross-react with other flaviviral infection and vaccination
West Nile virus	Serum ELISA & PRNT or PCR			ELISA may cross-react with other flaviviral infection and vaccination
Tick-borne encephalitis virus	Serum ELISA for IgM			
St. Louis virus	Serum ELISA for IgM, high titre of antibodies on HI (>1:320), CF (>1:128), IF (>1:256) or PRNA (>1:160)			
LaCrosse virus	Serum ELISA for IgM, 4X rise CF, HI or IF IgG titre			
Alphaviruses (Western, Venezuelan and Eastern equine encephalitis and Chikungunya viruses)	Serum ELISA, HI, PRNT or IF			
Nipah	Serum ELISA IgM	91.7	91.8	May cross-react with Hendra viral infection
Murray Valley encephalitis virus	Serum ELISA			

Table 15.8 (continued)

Infection	Test	Sensitivity (%)	Specificity (%)	Note
Kunjin virus	Serum ELISA			May cross-react with other flaviviral infection and vaccination
Hendra	Serum ELISA, nasopharyngeal aspirate PCR			ELISA may cross-react with Nipah viral infection
Dengue virus	Serum MAC-ELISA	90	98	May cross-react with other flaviviral infection and vaccination
	Serum RT-PCR	80–90	98	
Rift River Valley Virus	Serum ELISA for IgM			
Human herpesvirus 6	Serum ELISA for IgM or PCR			
Herpes B virus	Serum ELISA, PCR, Western blot, viral culture			
Kyasanur forest virus	Serum ELISA for IgM, HI, RT-PCR			ELISA may cross-react with Far Eastern tick-borne encephalitis and Al-Khumra viral infection
Al-Khumra virus	Serum ELISA for IgM			May cross-react with Far Eastern tick-borne encephalitis and Kyasanur forest viral infection
Hantavirus	Serum ELISA for IgM	97.2	~100	
	RT-PCR			Useful in acute infection before seroconversion
	PRNT and immunoblot			

Note: *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction, *ELISA* enzyme-linked immunosorbent assay, *PRNT* plaque reduction neutralization test, *HI* hemagglutination inhibition, *IF* immunofixation, *CF* complement fixation, *MAC-ELISA*, *IgM* antibody capture enzyme-linked immunosorbent assay, *RT-PCR* reverse transcriptase polymerase chain reaction

Brain Biopsy

Brain biopsy is the gold standard for the diagnosis of herpes simplex encephalitis, with a sensitivity of 95–99% and a specificity of 100%. Brain biopsy is also a definitive way to diagnose rabies but is not practical for an ante-mortem diagnosis. With the availability of PCR and the serological test, brain biopsy is now seldom done. Brain biopsy may be indicated in other infections, especially if other treatable conditions cannot be excluded by non-invasive tests.

Therapy

Initial Management

Patients presenting with viral encephalitis should be evaluated urgently and their airway, breathing and circulation assessed. The patient, if drowsy, should be positioned properly in a left lateral position to avoid aspiration. Intravenous access should be immediately secured and blood sent for important investigations, including serum electrolytes, sugar, creatinine, liver and thyroid function tests, full blood count and cultures. A chest X-ray should be performed promptly. Where there is clinical suspicion, a peripheral blood film, toxicology screen, clotting profile and D-dimer, urine porphyrin, urine and serum copper levels, serum caeruloplasmin level, erythrocyte sedimentation rate or C-reactive protein and autoimmune markers, such as antinuclear antibody and anti-neutrophil cytoplasmic antibody, should be estimated. In areas where certain infections are common, tests such as thick and thin blood film to test for malaria parasites, as well as culture, serological and other tests for HIV, syphilis, typhoid fever, tuberculosis, mycoplasma and other locally prevalent infections (Table 15.1) should be performed. Although not always necessary before lumbar puncture, CT scan of the brain with contrast enhancement should be done if there is suspicion of brain abscess, or CT venogram should be carried out for suspected venous sinus thrombosis. MRI is more sensitive in diagnosing viral encephalitis and to exclude important differential diagnoses such as acute disseminated encephalomyelitis, toxoplasmosis and vasculitides. Since herpes simplex virus is the commonest cause of sporadic encephalitis and, if left untreated, the mortality rate is in excess of 70%, patients on viral encephalitis should be started empirically on intravenous acyclovir 10 mg/kg thrice a day. If the diagnosis is confirmed by PCR or the serological test, acyclovir should be given for a total of 14 days; otherwise, the patient is at risk for recurrence. If the cause is another viral agent, acyclovir can be stopped and an appropriate antiviral, if available, started (Tables 15.9 and 15.10). The use of steroids in viral encephalitis is not proven.

Complications and Supportive Measures (Table 15.11)

Supportive measures and the treatment and prevention of complications are probably the most important aspects of the management of viral encephalitis. The complications of viral encephalitis are those caused by the virus and those secondary to the patient's poor state of consciousness. The most important complications directly related to the encephalitic process are focal deficits, behavioural disturbances and seizures. Major tranquillizers may be necessary in aggressive patients, though these should be used sparingly. Agents with a sedative effect should be avoided, since they may interfere with neurological assessment. Intramuscular administration of haloperidol at 2.5–10 mg is usually sufficient. An EEG is also often necessary to differentiate confusion from seizures, including non-convulsive status epilepticus. Convulsive seizures should be treated urgently, and if the seizure persists for more

Table 15.9 Specific antiviral therapy in viral encephalitis

Infection	Treatment	Class of evidence
Herpes simplex virus [14]	Acyclovir 10 mg/kg/d thrice a day i.v. for 10–14 days (reduce dosage in patients with renal failure)	AI
Varicella zoster virus [14]	Acyclovir 800 mg, five times a day i.v. for 7–10 days OR Ganciclovir 5 mg/kg twice a day i.v. for 7–10 days OR Famciclovir 500 mg thrice a day i.v. for 7 days OR Valacyclovir 1 g thrice a day i.v. for 7 days	BIII CIII
Cytomegalovirus [14]	Ganciclovir 5 mg/kg twice a day i.v. for 7–10 days <i>with/without</i> foscarnet 60 mg/kg thrice a day i.v. for 7–10 days	BIII
Herpes B virus [50]	<i>Post-exposure prophylaxis:</i> Wound cleansing AND EITHER Valacyclovir 1 g oral thrice a day for 2 weeks OR Acyclovir 800 mg oral five times a day for 2 weeks <i>Treatment</i> <i>Asymptomatic:</i> Acyclovir 12.5–15 mg/kg i.v. thrice a day for at least 14 days AND > 2 sets of culture negative <i>Symptomatic:</i> Ganciclovir 5 mg/kg i.v. twice a day for at least 14 days AND > 2 sets of culture negative THEN either stop or change to post-exposure oral prophylaxis for 6–12 months	CIII CIII CIII CIII CIII
Human herpes [6] virus [14] Enterovirus [51]	Foscarnet 60 mg/kg thrice a day i.v. for 2 weeks OR Ganciclovir 5 mg/kg twice a day i.v. for 2 weeks Pleconaril 5 mg/kg thrice a day i.v. for 10 days	BIII (immunocompetent) CIII (immunocompromised) CIII
Nipah virus [52]	Ribavirin 30 mg/kg loading, then 16 mg/kg four times a day i.v. for 4 days, then 8 mg/kg thrice a day i.v. for 3 days OR Ribavirin 2 g orally on day 1; 1.2 g thrice a day orally on day 2–4; 1.2 g twice a day orally on day 5–6; 600 mg twice a day orally on day 7–10	CIII
West Nile virus [53]	West Nile virus i.v. immunoglobulin 500 mg infusion daily for 6 days	Single case report
St. Louis virus [14, 54]	Alpha interferon-2b 3 muscular i.v., 3 muscular subcutaneous 12 h later; then every 24 h for 14 days	CIII
Hantaviral haemorrhagic fever with renal syndrome [55]	Ribavirin i.v. 33 mg/kg loading, 16 mg/kg every 6 h for 4 days, 8 mg/kg every 3 h for 3 days	BI

(continued)

Table 15.9 (continued)

Infection	Treatment	Class of evidence
Rabies and bat lyssavirus [56]	<p>All wounds should be swabbed for bacterial culture, thoroughly cleansed with soap and water and then irrigated with virucidal agent such as povidone–iodine solution. Give tetanus toxoid and antibiotics for Gram negatives and anaerobes</p> <p><i>If not previously vaccinated:</i></p> <ol style="list-style-type: none"> 1. Administer human rabies immunoglobulin 20 IU/kg. If possible, infiltrate the full dose around and into the wounds; if not, the remaining volume administered intramuscularly at sites distant from vaccine administration 2. Human diploid cell or purified chick embryo cell vaccine 1 mL i.m. in deltoid (or lateral thigh in small children) on day 0, 3, 7 and 14. If immunosuppressed, administer an extra dose on day 28. Do not administer into gluteal region <p><i>If previously vaccinated with tissue culture rabies vaccine or if vaccinated with older vaccine and has documented adequate antibodies response:</i></p> <ol style="list-style-type: none"> 1. Human rabies immunoglobulin should <i>not</i> be used 2. Administer human diploid cell or purified chick embryo cell vaccine 1 mL i.m. in deltoid (or lateral thigh in small children) on day 0 and on contralateral deltoid on day 3. Do not administer into gluteal region 	CIII

i.v. intravenous, *i.m.* intramuscular

than 5 min, the patient should be treated as a case of status epilepticus [57]. In herpes simplex encephalitis, Nipah encephalitis and furious rabies, autonomic dysfunction is a known complication. While hypotension needs to be treated with either fluid loading or inotropes, tachycardia and hypertension, unless very severe, may only need to be observed as the patient may become hypotensive suddenly. This is especially true in Nipah encephalitis. In some viral infections, concurrent systemic complications cause most of the fatality, requiring aggressive supportive measures. For example, in filoviral and arenaviral infections, haemorrhagic complications cause most of the fatality. Similarly, meningoencephalitis may be a late manifestation of Rift Valley fever virus, but it is the hepatic failure, renal failure and haemorrhagic complications that are often the cause of mortality. These patients require supportive treatment, including renal replacement therapy [58]. Other viruses may have concurrent lung involvement, and such patients may need oxygen therapy or even mechanical ventilation (Table 15.4). Some complications in viral encephalitis are related to the patient's state of consciousness. In comatose patients, aspiration or orthostatic pneumonia, deep vein thrombosis and pulmonary embolism, urinary tract infection and pressure sores are potential complications. These can be prevented by the use of a ripple mattress, frequent changes of position, heparin

Table 15.10 Common side effects and drug–drug interactions of antiviral drugs

Drug	Side effects	Interaction
Acyclovir	Nausea, vomiting, diarrhoea Headache, malaise Confusion, ataxia, tremor, drowsiness, seizure Anaemia, leucopenia, thrombocytopenia Hepatitis, vasculitis, Stevens–Johnson syndrome, renal failure	Probenecid increases the half-life of acyclovir
Ganciclovir	Anaemia, leucopenia, thrombocytopenia Infertility in men, teratogenicity Renal impairment, phlebitis Potential carcinogenesis	Ganciclovir increases didanosine levels. Probenecid and zidovudine increase level of oral ganciclovir. May interact with drugs that cause marrow suppression
Famciclovir	Headache, paraesthesiae Nausea, vomiting, diarrhoea Anaemia, leucopenia, hepatitis	Probenecid may increase the half-life of famciclovir
Valacyclovir	Thrombotic thrombocytopenic purpura Acute renal failure Seizure, confusion, encephalopathy Anaemia, hepatitis, rash, diarrhoea	No known significant drug interaction
Foscarnet	Acute renal failure Hypocalcaemia, hypo- or hyperphosphataemia, hypomagnesaemia, hypokalaemia Seizure, fever, anaemia, nausea, diarrhoea Marrow suppression Headache, malaise, giddiness, anorexia, rash, confusion, tremor, ataxia, cardiac conduction abnormalities, hepatitis	Interacts with ganciclovir. Severe hypocalcaemia if used with pentamidine; increased risk of renal failure when used together with aminoglycoside, amphotericin B, pentamidine, ritonavir, saquinavir
Ribavirin	Severe teratogenicity and embryocidal effect Anaemia, hepatic decompensation Urticaria, angioedema, anaphylaxis Stevens–Johnson syndrome, pneumonitis Confusion, fatigue, somnolence	May increase level of didanosine

prophylaxis, frequent change of the urinary catheter and meticulous nursing and physiotherapy. Patients who have a poor state of consciousness will also need assisted ventilation to prevent aspiration pneumonia and respiratory failure, as well as barrier nursing to prevent nosocomial infections. Rarely, viral encephalitic patients have a markedly raised intracranial pressure requiring treatment. This can be treated by raising the head end of the bed to 60°, assisted hyperventilation with arterial carbon dioxide partial pressure targeted to 30 mmHg and 200 cc of 20% mannitol infusion every 5 h for a maximum of 48 h. Beyond this, rebound rise in intracranial pressure may occur. CSF diversion procedures or decompressive surgery may be considered where necessary, appropriate and feasible. Other side effects of mannitol therapy include fluid overload, electrolytes and osmolality disturbances.

Table 15.11 Complications of viral encephalitides and their management

Complications	Prevention/ treatment
Behavioural changes	Haloperidol 2.5–10 mg i.m. or oral
Seizure	Midazolam 5–20 mg i.v. OR phenytoin 20 mg/kg i.v. at 50 mg/min, then 250 mg daily
Hypotension (from autonomic dysfunction or bleeding)	Rehydration, central venous pressure and renal function monitoring
Aspiration or orthostatic pneumonia	Chest physiotherapy, endotracheal intubation and mechanical ventilation in comatose patients, antibiotics
Deep vein thrombosis	Heparin prophylaxis, anti-embolism stockings
Pressure sores	Ripple mattress, 2-h positional changes, wound dressing
Raised intracranial pressure	Mannitol infusion before cerebrospinal fluid diversion or decompressive surgery
Spasticity	Mild: Baclofen (10–30 mg oral thrice a day) or gabapentin (300–900 mg oral thrice a day) Severe focal: Botulinum toxin Severe diffuse: Intrathecal baclofen infusion
Chorea and dyskinesia	Benzhexol (1–10 mg oral thrice a day)

Rehabilitation

Even though most patients with viral encephalitis recover fully, a significant proportion of patients develop long-term neurological sequelae. Physiotherapy and occupational therapy are important in the rehabilitation of patients who have weakness, spasticity and cognitive impairment, as well as in the prevention of joint contractures. For spasticity, baclofen (10–30 mg thrice a day orally) and gabapentin (300–900 mg thrice a day orally) are moderately effective. For focal spasticity, botulinum toxin injection is the most effective treatment, while intrathecal baclofen infusion can be used in patients with more generalized spasticity who fail oral therapy. In patients with chorea and dyskinesia, benzhexol, at a dosage of 1–10 mg thrice a day, is the first line of treatment. The dosage of all these medications should be kept low to avoid cognitive and other side effects. None of these treatments, however, has been tested in a randomized controlled trial.

Prognosis

Overall, the prognosis of viral encephalitides is moderately good; the fatality rate ranges from 4 to 9%, and 25 to 55% of the patients develop neurological sequelae. The commonest sequelae are seizures, developmental delay in children, headache, emotional changes, intellectual impairment, cranial nerve palsy, speech disorders and ataxia [59, 60]. However, the prognosis depends, to a large extent, on the underlying aetiological agent and host factors, especially age. The outcome is poorer in the extremes of age, especially children in Japanese, Eastern equine and Western

equine encephalitides and the elderly in St. Louis, West Nile, Eastern equine and Nipah encephalitides. Mortality is especially high in encephalitis caused by the herpes simplex virus (>70%), B virus (80%), Marburg virus (65–75%), Ebola virus (65–100%), Nipah virus (32–73%), Hendra virus (50%), and Eastern equine encephalitis virus (20–80%). More than 97% of the survivors of untreated herpes simplex encephalitis and 70% of Eastern equine encephalitis survivors have residual neurological deficits [42, 50, 61–63].

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Chronic Meningitis

16

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Introduction

Meningeal inflammation is termed meningitis, and it may be acute or chronic, chronic being arbitrarily defined as lasting for more than 4 weeks [1]. The causes of meningitis may be both infectious and noninfectious. Some authors have a different opinion and have excluded chronic meningeal involvement in association with CNS mass lesions, pre-existing systemic diseases that are known to cause meningitis, and meningitis that may follow neurosurgical interventions from this diagnostic category [2]. However, this exclusion is considered to be too restrictive for clinical practice and is therefore not accepted as such. Chronic meningitis may be associated with cerebritis or encephalitis and involvement of the cerebral parenchyma with granulomatous infection, inflammation, or malignant infiltration. Also, complications such as hydrocephalus, vasculitic infarcts, and raised intracranial pressure may affect cranial nerves and spinal nerve roots and cause dysfunction of these structures too. Chronic meningitis may also affect the adjacent structures such as skull and dural venous sinuses and cause osteomyelitis or cerebral venous sinus thrombosis.

Chronic meningitis is a diagnosis which is often a test of the diagnostic armamentarium. It involves all aspects of diagnosis from history to physical examination along with laboratory support and a multidisciplinary approach which, in an individual patient, may include the neurologist, radiologist, ophthalmologist, pulmonologist, internist, neurosurgeon, pathologist, and microbiologist.

In this chapter, we will discuss the clinical approach to diagnosing chronic meningitis and then briefly outline the various investigational tools that help in

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confirming this diagnosis. Details about individual entities are beyond the scope of this chapter. The reader is referred to Chap. 17 of Volume II for some more details about tubercular and fungal meningitis.

Classification

An etiological classification of chronic meningitis should in no way be considered exhaustive. It simply helps in organizing some of the reported etiological entities in an orderly and retrievable manner so that one can run through this list of broad categories when faced with a patient and no category is inadvertently missed. The caveat in the published data on chronic meningitis stems from the fact that chronic meningitis, in most parts of the world, is not a very frequently encountered entity. Moreover, patients that have been reported are from wide-ranging geographical regions and populations and have presented to clinics, centers, or doctors who may vary widely in their individual understanding, exposure, and recognition of the disease. Descriptions are available mostly as case reports or at best as small, single-center retrospective case series. It is understandable then that etiological characterization of patients will be influenced by the region that patients are being reported from [3]. For example, any series of chronic meningitis being reported from India will have patients of tuberculous meningitis outnumber all other etiological entities.

Causes of chronic meningitis may be broadly categorized and listed as follows. In most reported series, the exact etiology remains unestablished in as many as one-third of patients despite extensive investigations [3].

Infectious Causes

Mycobacterial

Mycobacterium tuberculosis, nontubercular mycobacteria.

Bacterial

Nocardia, *Listeria*, *Brucella*, *Francisella tularensis*, *Actinomyces*, *Ehrlichia chaffeensis*, Whipple's disease.

Spirochetal

Borrelia burgdorferi, *Treponema pallidum*, *Leptospira*.

Fungal

Cryptococcus, *Histoplasma*, *Coccidioides*, *Blastomycetes*, *Aspergillus*, *Sporothrix*.

Parasitic

Taenia solium (cysticercosis), *Toxoplasma*, *Acanthamoeba*, *Schistosoma*, *Angiostrongylus*.

Viral

Human immunodeficiency virus, herpes simplex virus, varicella zoster virus, Epstein–Barr virus, *Cytomegalovirus*, *Enterovirus*, human T cell lymphotropic virus I and II.

Noninfectious Causes**Associated with Systemic Diseases**

Systemic lupus erythematosus, Behcet's disease, Sarcoidosis, Fabry disease, Sjogren's disease, primary CNS vasculitis like granulomatous angiitis of the CNS and eosinophilic vasculitis of the CNS or vasculitis associated with systemic diseases like granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, Vogt-Koyanagi-Harada syndrome (VKHS).

Malignancy Related

Leptomeningeal lymphomatosis, carcinomatous meningitis.

Chemical Causes

Drug-induced (NSAIDs, IVIg), intrathecal injections (antibiotics, antitumor drugs, anesthetic agents), ruptured intracranial cysts.

Idiopathic

In up to one-third of the cases, no etiology may be established in spite of extensive investigations [4].

Evaluation of Patients with Chronic Meningitis

The approach to a patient with chronic meningitis, like any other patient in medicine, begins with a comprehensive history and physical examination.

History

This may be the most difficult and time-consuming part of the diagnostic process. Patients may not be able to give a satisfactory history due to neurologic impairment. Sometimes patients may not realize the importance or relevance of events that may have occurred in the distant past. At other times, crucial events may not have been perceived by the patient to be of any consequence at all. All this makes history taking in a patient of chronic meningitis a time-consuming and difficult exercise. One may even need to keep returning to the patient or the caregivers for unreported elements in the history that may not have emerged in the first attempt. Important components to be noted in the history include duration of the illness, onset and progression of the disease, past history including all systemic illnesses such as cancer, transplantation of hematopoietic stem cells and solid organs, and multisystem inflammatory diseases under the rheumatology spectrum [5]. Particular emphasis

should be paid to drug history (drug-induced meningitis, IV drug use and related diseases, chronic immunosuppressive medication), social and occupational history (history of high-risk sexual behavior, persons living alone, exposure to tuberculosis patients, immunocompromised status), and history of travel. Certain infections may be acquired by travel to areas where these are endemic such as tuberculosis in developing countries and dimorphic fungal infections in North America. Sometimes, the travel may not even be very recent and yet be of significance. Travel to an endemic region is also likely to remain unreported if the patient only passed through the area and spent a few hours at the airport. However, this short time may have been enough for him or her to have picked up an infection. Infections such as tuberculosis and cryptococcosis are much more common in immunocompromised patients with impaired cell-mediated immunity such as HIV infection, hematologic malignancy, or transplant recipients.

Clinical Features

The classical triad of fever, headache, and vomiting may be present in chronic meningitis too, but the time line may just be more protracted and last weeks to months. Many other clinical features may also be encountered (Table 16.1). These range from an indolent presentation with mild headache with personality changes to fulminant presentations with focal neurologic signs and obtundation which may also be fatal if not diagnosed and treated promptly.

Beyond the usual history and examination, patients of chronic meningitis may need some other specific clinical evaluation before one proceeds to investigate them.

Table 16.1 Symptoms and signs in chronic meningitis

<i>Symptoms</i>
Headache
Pains and aches (due to radicular involvement)
Vomiting and nausea
Photophobia
Seizures
Fever
Constitutional symptoms (anorexia, loss of weight, night sweats)
Focal deficits/movement disorders
<i>Neurologic signs</i>
Neck stiffness
Papilledema
Focal neurologic signs
Cranial nerve palsies
Hemiparesis/monoparesis
Paraparesis
Urinary retention
Altered sensorium
Drowsiness
Coma

Systemic Examination

Ocular Examination

Anterior chamber examination: Examination with a slit lamp to look for iridocyclitis (sarcoidosis, Behcet's disease, Vogt-Koyanagi-Harada syndrome VKHS), lymphoma deposits.

Fundus: To look for retinal deposits of lymphoma, choroidal tubercles in tuberculosis, retinal vasculitis, retinal detachment (in VKHS, tuberculosis), fundus features of candida abscesses.

Examination of the Nostrils, Pharynx, and Middle Ear

Clinical examination including endoscopic examination to look for rhinosinusitis in case of fungal infections, granulomatous inflammatory diseases (granulomatosis with polyangiitis), lymphoma.

Examination of the Skin and Genitalia

Skin lesions are common in fungal infections such as cryptococcus, histoplasma, and blastomycosis. Sarcoidosis can present with erythema nodosum. Secondary syphilis may have characteristic erythematous rash involving palms and soles. Hematologic malignancies may have subcutaneous and dermal deposits. Melanoma with leptomeningeal metastasis may be missed if detailed dermatologic examination is not carried out. External genitalia should always be examined to look for testicular enlargement suggesting hematologic malignancies and germ cell tumors. Genital ulcers are noted in Behcet's disease, various sexually transmitted infections, as well as scar denoting previous chancre of syphilis may be the clue to diagnosis.

Investigations

Imaging

Neuroimaging

The timing of imaging and whether it should precede or follow lumbar puncture varies in chronic meningitis as compared to acute meningitis. In most patients of chronic meningitis, it may be preferable to perform imaging first even in patients who present with a relatively acute presentation in the context of a more long-standing meningeal disease. MRI with contrast is the imaging modality of choice [6, 7], but a contrast-enhanced CT scan may be preferred in case an MRI is not available or there are other logistic issues in very sick patients. An MRI can detect exudates in the basal meninges as well as in the convexity. MRI FLAIR sequence is very sensitive for detection of exudates. Contrast enhancement occurs in infectious, inflammatory, as well as neoplastic infiltration, and the pattern of contrast enhancement varies from diffuse enhancement to focal and nodular enhancement. Contrast-enhancing regions may be of maximum diagnostic utility when biopsied. Findings

on an abnormal MRI may sometimes be non-specific. However, certain imaging characteristics and location of lesions may be diagnostic in cases such as tuberculomas, toxoplasmosis, cryptococcosis, and cysticercosis, though in most cases biopsy may still be needed to be definite. The MRI may also reveal hydrocephalus, infarcts, evidence of venous sinus thrombosis, aneurysms of vessels in case of infections such as brucella, and brainstem involvement in case of listeriosis, lymphomatosis, or Behcet's disease. A baseline CT or MRI may also be useful for periodically following up patients especially when the specific etiology cannot be established and empirical treatment has been initiated.

Imaging of the Chest/Abdomen

Imaging of chest and abdomen using X-ray or CT scan is invaluable to look for extraneuronal involvement such as in sarcoid, lymphoma, as well as various infections such as pulmonary involvement in tuberculosis, histoplasmosis, coccidioidomycosis, as well as inflammatory conditions such as granulomatosis with polyangiitis and sarcoidosis.

PET CT

PET CT may be useful to look for hypermetabolic foci in case of infections, [8] lymphoma, as well as noninfectious inflammatory causes such as sarcoidosis [9]. However, the features are non-specific. PET CT of the whole body may be helpful to look for dissemination of infection, evaluation of lungs, mediastinum, abdominal lesions such as lymphnodes, ileocecal involvement in tuberculosis, mass lesions, and to select biopsy site for maximum diagnostic yield. It can also differentiate from other diseases such as demyelination, in which there are no hypermetabolic foci.

CSF Examination

CSF examination is the cornerstone in the diagnostic workup of chronic meningitis. CSF examination is carried out under strict aseptic precautions. Before embarking on CSF examination, fundus examination to look for features of papilledema and imaging to look for mass lesions and signs of raised intracranial pressure and impending herniation are essential.

Though CSF examination is important, the procedure of obtaining CSF is not without risks. The procedure may lead to herniation in patients with mass effect [10, 11]. The risks of CSF drainage must be weighed against the presumed benefits of CSF examination, and if needed, urgent intracranial pressure-lowering efforts such as hyperventilation and osmotic diuresis may be instituted.

Occasionally empirical treatment with antitubercular or antifungal agents may need to be initiated, based on suspicions raised on neuroimaging, before lumbar puncture. Alternatively, CSF drainage procedures such as external ventricular drainage or ventriculoperitoneal shunting may be done following which CSF may be obtained for analysis. The findings of various investigations in chronic meningitis have been listed in Table 16.2.

Table 16.2 Findings on CSF examination in chronic meningitis

CSF examination	Comments
Opening pressure (normal 70–170 mm CSF)	Should always be measured; may be increased in tubercular, fungal, sarcoid meningitis, and neoplastic meningitis Has prognostic value
Cell count increased (>5/ μ L)	May be polymorphonuclear: In fungal infections, early stage of tubercular meningitis, brucella, nocardia neoplastic meningitis Lymphocytic: In most chronic meningitis Eosinophilic: In leukemic, parasitic infections CSF cell count may be normal in cryptococcal meningitis, often in immunosuppressed patients, and in neoplastic meningitis due to intermittent shedding of cells
Biochemistry	
CSF sugar (normal 60% of corresponding blood sugar)	Decreased or normal
CSF protein (normal < 45 mg/dL)	Usually increased
Tests for specific diagnosis	
Cytology for malignant cells	High volume of CSF (at least 10 mL) has to be sent for processing immediately after CSF drainage. Single sample has sensitivity of around 50% which increases to 90% with three samples [12]
Flow cytometry	In diagnosis of lymphoma/leukemia
Cryptococcal antigen testing, India ink staining Cryptococcal culture	India ink staining and cryptococcal antigen testing cannot be used to look for clinical improvement. Cryptococcal culture can be used for diagnosis as well as follow-up [13]
VDRL/RPR	Highly sensitive in secondary syphilis with aseptic meningitis, less sensitive in tertiary syphilis and especially in tabes dorsalis [14]
Fungal cultures and staining	Considered gold standard, however time-consuming and not useful for starting therapy
AFB staining and culture	AFB staining has poor sensitivity and culture takes a long time to grow and is not useful for diagnosis in the acute setting. Culture is invaluable in drug sensitivity testing [15]
Nucleic acid amplification tests (TB-PCR, Xpert MTB Rif)	Sensitivity of 0.56 and specificity of 0.98 [16] Can rule in, but not rule out tuberculosis
CSF ADA (for tuberculosis)	Not recommended due to the number of false positives including lymphoma and brucellosis, not sensitive in HIV-associated CNS TB [15]
Cultures for brucella/ nocardia	Lower sensitivity as compared to antibody testing [17]
Tube agglutination and Rose Bengal test (<i>Brucella</i>)	Serum studies of standard tube agglutination and Rose Bengal test are more sensitive than CSF studies; however, SAT and RBT give almost similar results [17]
Viral PCR-HSV, HZV, EBV, CMV	Have high sensitivity and specificity
ELISA/EITB for cysticercosis	Useful when imaging is not diagnostic. EITB is more specific than ELISA, while both are equally sensitive [18]
Toxoplasma PCR testing	May be done in CSF, useful adjunct to serology, and more sensitive [19]
CSF ACE level	Not specific; useful for monitoring response to treatment [20]

Blood Investigations

Blood investigations including hemogram, ESR, liver, and renal function tests may be abnormal when chronic meningitis is a consequence of a systemic disease or of an ongoing treatment for another entity such as a malignancy. These tests are also useful as a baseline for monitoring drug-induced adverse effects such as antitubercular drug- or voriconazole-induced hepatotoxicity, amphotericin B-induced renal dysfunction, etc. Serum LDH may be elevated in lymphoma but is non-specific. Peripheral smear examination is essential to look for leukemia in which it may be diagnostic or more commonly there may be non-specific hematological abnormalities such as anemia and an elevated ESR.

Serologic Testing

Serologic testing can play a vital role in the diagnosis of chronic meningitis but has to be used judiciously. Caveats applicable to serologic testing have been listed in Table 16.3.

Meningeal and Brain Biopsy

In spite of extensive noninvasive testing, a definitive etiological diagnosis is not possible in as many as 34% of patients of chronic meningitis [3]. In most reported series, a biopsy which may be meningeal or brain or a combination of meningeal and brain biopsies has met with some success. Meningeal biopsy is an invasive procedure and needs expertise and infrastructure for it to be performed. Moreover, it is not 100% sensitive, though it has high specificity in diagnosis. Many cases of chronic meningitis have non-specific inflammation, and definite diagnosis may not be possible even after biopsy [26]. So it is essential to choose patients undergoing meningeal biopsy wisely, so as to maximize the diagnostic yield. The most significant finding which predicted the yield of meningeal biopsy was gadolinium enhancement on MRI. This was demonstrated in a study of 37 patients where the biopsy was diagnostic in 80% patients who had an enhancing lesion on MRI as compared to only in 9% who did not have such a lesion [4]. Success reported from biopsies has varied, and decision to biopsy a patient or not should be made on a case-to-case basis. Most success can be anticipated when there are focal contrast-enhancing lesions on MRI that can be safely accessed by the surgeon. Brain biopsy of focal lesions may be diagnostic as well as useful for culture and sensitivity.

Treatment and Prognosis

Treatment is directed at the underlying disease. Treatment involves antibiotics, antitubercular or antifungal drugs in infections, steroids, and other immunosuppression in case of SLE, sarcoid, Behcet's or Sjogren's syndrome, and chemotherapy and radiation in case of neoplastic causes. Despite extensive evaluation, around 30% of

Table 16.3 Serological testing in chronic meningitis

Serologic testing	Comments
Fungal: <i>Histoplasma</i> antigen	Sensitivity in serum is close to 100% and urine is 75%
Cryptococcal antigen	Denotes the burden of disease; relates to extraneuronal involvement and dissemination [21]
<i>Aspergillus</i> : Beta galactomannan	Interpretation is difficult with many false positives, may be more useful in hematologic malignancy patients with invasive fungal infections [22, 23]
Candida beta 1, 3 glucan	May be positive in other fungal infections also [24]
Serum VDRL, TPHA	More sensitive than CSF testing. CSF VDRL-negative cases with serum positivity can still have neurosyphilis [14]
Serum brucella antigen ELISA, RBT, STA	More sensitive than CSF testing [17]
Lyme serology	ELISA is the first line followed by Western blot assay. If ELISA is negative, result is negative. If ELISA is positive, Western blot has to be carried out, and if negative, the test is considered to be negative [25]
Toxoplasma serology IgG and IgM	Positive IgG in immunocompromised host with appropriate imaging and clinical scenario is considered to be diagnostic. However, it may be false negative if the patient is unable to mount an immune response
HIV serology	Should be done in all patients with chronic meningitis
Noninfectious inflammatory diseases	
ANA, Anti-dsDNA	Systemic lupus erythematosus
c-ANCA, p-ANCA, anti-PR-3 ELISA, anti-MPO ELISA	Granulomatosis with polyangiitis
Anti-SSA, SSB	Sjogren's syndrome
Serum ACE	Sarcoidosis; neither sensitive nor specific [20]
Other clinical tests	
Tuberculin skin testing	Tuberculosis, anergy in sarcoidosis
Pathergy testing	Behcet's disease
Schirmer's test	Sjogren's syndrome
Biopsy of other sites	
Lip biopsy	Sjogren's syndrome
Lymph node biopsy	Tuberculosis, sarcoidosis, lymphoma, GPA, <i>Histoplasma</i> , and other fungi
Lung nodule biopsy	Tuberculosis, sarcoidosis, lymphoma, GPA, <i>Histoplasma</i> , and other fungi
Bone marrow examination	Tuberculosis, sarcoidosis, lymphoma <i>Histoplasma</i> , and other fungi

chronic meningitis may remain undiagnosed [27]. In such cases, empiric therapy may be instituted. Depending on the clinical probability and epidemiology, empiric antitubercular therapy or antifungal therapy may be appropriate. In areas where the prevalence of tuberculosis is high, an important therapeutic dilemma is regarding the use of ATT, either alone or in combination with corticosteroids. Steroids, it is

feared, may non-specifically act to provide transient improvement both in symptoms and in the radiological abnormalities. It is therefore extremely important to closely review all chronic meningitis patients both clinically and with interval imaging. In everyday clinical practice, we find patients who are very sick and may need treatment to be started urgently even before an optimal evaluation can be completed.

Conclusion

Chronic meningitis requires a systematic approach for diagnosis, and even after extensive investigations, the etiologic diagnosis may remain elusive. Regular follow-up and response to treatment along with pursuing potential diagnostic clues with repeated clinical, radiologic, microbiologic, and CSF examination may be essential.

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